

VANILLOID RECEPTOR LIGANDS AND THEIR USE IN TREATMENTS

This application claims the benefit of U.S. Provisional Application No.
5 60/446,511, filed February 10, 2003, which is hereby incorporated by reference.

Background

The vanilloid receptor 1 (VR1) is the molecular target of capsaicin, the active ingredient in hot peppers. Julius et al. reported the molecular cloning of
10 VR1 (Caterina et al., 1997). VR1 is a non-selective cation channel which is activated or sensitized by a series of different stimuli including capsaicin and resiniferatoxin (exogenous activators), heat & acid stimulation and products of lipid bilayer metabolism, anandamide (Premkumar et al., 2000, Szabo et al., 2000, Gauldie et al., 2001, Olah et al., 2001) and lipoxygenase metabolites (Hwang et al.,
15 al., 2000). VR1 is highly expressed in primary sensory neurons (Caterina et al., 1997) in rats, mice and humans (Onozawa et al., 2000, Mezey et al., 2000, Helliwell et al., 1998, Cortright et al., 2001). These sensory neurons innervate many visceral organs including the dermis, bones, bladder, gastrointestinal tract and lungs; VR1 is also expressed in other neuronal and non-neuronal tissues
20 including but not limited to, CNS nuclei, kidney, stomach and T-cells (Nozawa et al., 2001, Yiangou et al., 2001, Birder et al., 2001). Presumably expression in these various cells and organs may contribute to their basic properties such as cellular signaling and cell division.

Prior to the molecular cloning of VR1, experimentation with capsaicin
25 indicated the presence of a capsaicin sensitive receptor, which could increase the activity of sensory neurons in humans, rats and mice (Holzer, 1991; Dray, 1992, Szallasi and Blumberg 1996, 1999). The results of acute activation by capsaicin in humans was pain at injection site and in other species increased behavioral sensitivity to sensory stimuli (Szallasi and Blumberg, 1999). Capsaicin
30 application to the skin in humans causes a painful reaction characterized not only by the perception of heat and pain at the site of administration but also by a wider area of hyperalgesia and allodynia, two characteristic symptoms of the human

condition of neuropathic pain (Holzer, 1991). Taken together, it seems likely that increased activity of VR1 plays a significant role in the establishment and maintenance of pain conditions. Topical or intradermal injection of capsaicin has also been shown to produce localized vasodilation and edema production (Szallasi and Blumberg 1999, Singh et al., 2001). This evidence indicates that capsaicin through its activation of VR1 can regulate afferent and efferent function of sensory nerves. Sensory nerve involvement in diseases could therefore be modified by molecules which effect the function of the vanilloid receptor to increase or decrease the activity of sensory nerves.

VR1 gene knockout mice have been shown to have reduced sensory sensitivity to thermal and acid stimuli (Caterina et al., 2000)). This supports the concept that VR1 contributes not only to generation of pain responses (i.e. via thermal, acid or capsaicin stimuli) but also to the maintenance of basal activity of sensory nerves. This evidence agrees with studies demonstrating capsaicin sensitive nerve involvement in disease. Primary sensory nerves in humans and other species can be made inactive by continued capsaicin stimulation. This paradigm causes receptor activation induced desensitization of the primary sensory nerve - such reduction in sensory nerve activity *in vivo* makes subjects less sensitive to subsequent painful stimuli. In this regard both capsaicin and resiniferatoxin (exogenous activators of VR1), produce desensitization and they have been used for many proof of concept studies in *in vivo* models of disease (Holzer, 1991, Dray 1992, Szallasi and Blumberg 1999).

Bibliography

Birder-LA. Kanai-AJ. de-Groat-WC. Kiss-S. Nealen-ML. Burke-NE. Dineley-KE. Watkins-S. Reynolds-IJ. Caterina-MJ. (2001) Vanilloid receptor expression suggests a sensory role for urinary bladder epithelial cells. PNAS 98: 23: 13396-13401.

Caterina, M.J, Schumacher, M.A., Tominaga, M., Rosen, T.A., Levine, J.D., and Julius, D, (1997). The capsaicin receptor: a heat-activated ion channel in the pain pathway. Nature 389: 816-824.

Caterina-MJ. Leffler-A. Malmberg-AB. Martin-WJ. Trafton-J. Petersen-Zeitze KR. Koltzenburg-M. Basbaum-AI. Julius-D (2000) Impaired nociception and

pain sensation in mice lacking the capsaicin receptor. *Science*-(WASH-DC). 288: 5464: 306-313.

Cortright-DN. Crandall-M. Sanchez-JF. Zou-T. Krause-JE.

White-G (2001) The tissue distribution and functional characterization of human
5 VR1. *Biochemical and Biophysical Research Communications* 281: 5: 1183-1189

Dray, A., (1992). Therapeutic potential of capsaicin-like molecules. *Life Sciences* 51: 1759-1765.

Gauldie-SD. McQueen-DS. Pertwee-R. Chessell-IP. (2001) Anandamide
10 activates peripheral nociceptors in normal and arthritic rat knee joints. *British Journal of Pharmacology* 132: 3: 617-621.

Helliwell-RJA. McLatchie-LM. Clarke-M. Winter-J. Bevan-S.

McIntyre-P (1998) Capsaicin sensitivity is associated with expression of the
vanilloid (capsaicin) receptor (VR1) mRNA in adult rat sensory
15 ganglia. *Neuroscience Lett.* 250: 3: 177-180.

Holzer, P. (1991) Capsaicin: Cellular targets, Mechanisms of Action and
selectivity for thin sensory neurons. *Pharmacological reviews* 43: 2: 143-201

Hwang-SW. Cho-H. Kwak-J. Lee-SY. Kang-CJ. Jung-J. Cho-S.

Min-KH. Suh-YG. Kim-D. Oh-U. (2000) Direct activation of capsaicin
20 receptors by products of lipoxygenases: Endogenous capsaicin-like substances.
PNAS 97: 11: 6155-6160.

Mezey-E. Toth-ZE. Cortright-DN. Arzubi-MK. Krause-JE. Elde-R.

Guo-A. Blumberg-PM. Szallasi-A (2000) Distribution of mRNA for vanilloid
receptor subtype 1 (VR1), and VR1-like immunoreactivity, in the central nervous
25 system of the rat and human.
PNAS 97: 7: 3655-3660.

Nozawa-Y. Nishihara-K. Yamamoto-A. Nakano-M. Ajioka-H.

Matsuura-N.(2001) Distribution and characterization of vanilloid receptors in the
rat stomach. *Neuroscience Letters* 309: 1: 33-36.

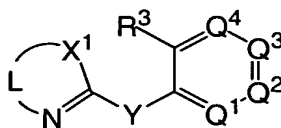
30 Olah-Z. Karai-L. Iadarola-MJ. (2001) Anandamide activates vanilloid receptor 1
(VR1) at acidic pH in dorsal root ganglia neurons and cells ectopically expressing
VR1. *Journal of Biological Chemistry* 276: 33, 31163-31170.

- Onozawa-K. Nakamura-A. Tsutsumi-S. Yao-J. Ishikawa-R.
Kohama-K. (2000) Tissue distribution of capsaicin receptor in the various organs
of rats. *Proc. Jpn. Acad. Ser. B, Phys.-Biol. Sci.* 76: 5: 68-72.
- Premkumar-LS. Ahern-GP. (2000) Induction of vanilloid receptor channel
5 activity by protein kinase C. *Nature (London)* 408: 6815: 985-990.
- Singh-LK. Pang-X. Alexacos-N. Letourneau-R. Theoharides-TC. (1999) Acute
immobilization stress triggers skin mast cell degranulation via corticotropin
releasing hormone, neurotensin, and substance P: A link to neurogenic skin
disorders. *Brain Behav. Immun.* 13: 3: 225-239.
- 10 Szallasi, A. Blumberg-PM (1996) Vanilloid receptors: New insights enhance
potential as a therapeutic target. *Pain* 68: 195-208
- Szallasi-A. Blumberg-PM. (1999) Vanilloid (capsaicin) receptors and
mechanisms. *Pharmacol. Rev.* 51: 2: 159-211.
- Szabo-T. Wang-J. Gonzalez-A. Keddi-N. Lile-J. Treanor-J. Blumberg-PM.
15 (2000) Pharmacological characterization of the human vanilloid receptor type-1
(hVR1). *Society for Neuroscience Abstracts.* 26:1-2: 634.18.
- Tominaga, M., Caterina, M.J., Malmberg, A.B., Rosen, T.A., Gilbert, H., Skinner,
K., Raumann, B.E., Basbaum, A.I., and Julius, D., (1998). The cloned capsaicin
receptor integrates multiple pain-producing stimuli. *Neuron* 21: 531-543.
- 20 Yiangou-Y. Facer-P. Dyer-NHC. Chan-CLH. Knowles-C.
- Williams-NS. Anand-P. (2001) Vanilloid receptor 1 immunoreactivity in
inflamed human bowel. *Lancet (North American Edition)* 357: 9265: 1338-1339.
- Yiangou-Y. Facer-P. Ford-A. Brady-C. Wiseman-O. Fowler-CJ.
- Anand-P. (2001) Capsaicin receptor VR1 and ATP-gated ion channel P2X3 in
25 human urinary bladder. *BJU International* 87: 9: 774-779.
- Wang-H. Bian-D. Zhu-D. Zajic-G. Loeloff-R. Lile-J. Wild-K. Treanor-J.
Curran-E. (2000) Inflammation-induced upregulation of VR1 in rat spinal cord
and DRG correlates with enhanced nociceptive processing. *Society for
Neuroscience Abstracts* 26:1-2: 632.15.

Summary

The present invention comprises a new class of compounds useful in the treatment of diseases, such as vanilloid-receptor-mediated diseases and other maladies, such as inflammatory or neuropathic pain and diseases involving sensory nerve function such as asthma, rheumatoid arthritis, osteoarthritis, inflammatory bowel disorders, urinary incontinence, migraine and psoriasis. In particular, the compounds of the invention are useful for the treatment of acute, inflammatory and neuropathic pain, dental pain, general headache, migraine, cluster headache, mixed-vascular and non-vascular syndromes, tension headache, general inflammation, arthritis, rheumatic diseases, osteoarthritis, inflammatory bowel disorders, inflammatory eye disorders, inflammatory or unstable bladder disorders, psoriasis, skin complaints with inflammatory components, chronic inflammatory conditions, inflammatory pain and associated hyperalgesia and allodynia, neuropathic pain and associated hyperalgesia and allodynia, diabetic neuropathy pain, causalgia, sympathetically maintained pain, deafferentation syndromes, asthma, epithelial tissue damage or dysfunction, herpes simplex, disturbances of visceral motility at respiratory, genitourinary, gastrointestinal or vascular regions, wounds, burns, allergic skin reactions, pruritus, vitiligo, general gastrointestinal disorders, gastric ulceration, duodenal ulcers, diarrhea, gastric lesions induced by necrotising agents, hair growth, vasomotor or allergic rhinitis, bronchial disorders or bladder disorders. Accordingly, the invention also comprises pharmaceutical compositions comprising the compounds, methods for the treatment of vanilloid-receptor-mediated diseases, such as inflammatory or neuropathic pain, asthma, rheumatoid arthritis, osteoarthritis, inflammatory bowel disorders, urinary incontinence, migraine and psoriasis diseases, using the compounds and compositions of the invention, and intermediates and processes useful for the preparation of the compounds of the invention.

The compounds of the invention are represented by the following general structure:

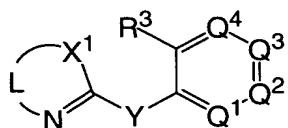


or a pharmaceutically acceptable salt thereof, wherein L, N, Q¹, Q², Q³, Q⁴, R³, X¹ and Y are defined below.

The foregoing merely summarizes certain aspects of the invention and is not intended, nor should it be construed, as limiting the invention in any way. All patents, patent applications and other publications recited herein are hereby incorporated by reference in their entirety.

Detailed Description

One aspect of the current invention relates to compounds having the general structure:



or any pharmaceutically-acceptable salt thereof, wherein:

L is -C(R¹)=C(R²)- or -C(R²)=C(R¹)-;

Q¹ is N or C(R⁵);

Q² is N or C(R⁶);

Q³ is N or C(R⁷);

Q⁴ is N or C(R⁶);

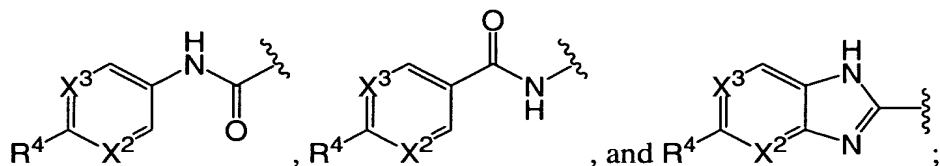
X¹ is NH, S, S=O, S(=O)₂ or O;

X² is N or C(R⁸);

X³ is N or C(R⁹);

Y is NH, C(R¹⁰)(R¹¹), O, S, S(=O), S(=O)₂ or C(=O);

R¹ is selected from



R² is H, C₁₋₂alkyl, -CF₃, -NH₂, -OH, -OCH₃, F, Cl or Br;

R³ is halo, C₁₋₆alkyl, C₁₋₄haloalkyl, -N(H)C₁₋₄alkyl, -N(C₁₋₄alkyl)C₁₋₄alkyl or -OC₁₋₄alkyl;

R^4 is Br, I, C_{2-6} alkyl, C_{1-4} haloalkyl, $-C(=O)R^b$, $-OR^b$, $-(C_{1-4}haloalkyl)OH$, $-N(C_{1-2}alkyl)C_{1-2}alkyl$ or $-CN$; wherein if Y is CH_2 and R^3 and R^5 are both Cl, then R^4 is other than isopropyl;

R^5 is, independently in each instance, H, halo, C_{1-6} alkyl, C_{1-4} haloalkyl,
5 $-N(H)C_{1-4}alkyl$, $-N(C_{1-4}alkyl)C_{1-4}alkyl$ or $-OC_{1-4}alkyl$;

R^6 is, independently in each instance, H, F, C_{1-6} alkyl, C_{1-4} haloalkyl,
 $-N(R^a)R^a$, $-OR^a$, $-S(=O)_2N(R^a)R^a$, $-C(=O)N(R^a)R^a$, or $-N(R^a)C(=O)R^b$;

R^7 is H, F, C_{1-6} alkyl, C_{1-4} haloalkyl, $-N(R^a)R^a$, $-OR^a$, $-S(=O)_2N(R^a)R^a$,
 $-C(=O)N(R^a)R^a$, or $-N(R^a)C(=O)R^b$;

10 R^8 is H, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, $-N(H)C_{1-4}alkyl$,
 $-N(C_{1-4}alkyl)C_{1-4}alkyl$ or $-OC_{1-4}alkyl$;

R^9 is H, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, $-N(H)C_{1-4}alkyl$,
 $-N(C_{1-4}alkyl)C_{1-4}alkyl$ or $-OC_{1-4}alkyl$;

R^{10} is H, F, C_{1-6} alkyl, C_{1-4} haloalkyl, $-N(R^a)R^a$, or $-OR^a$;

15 R^{11} is H, F, C_{1-6} alkyl, C_{1-4} haloalkyl, $-N(R^a)R^a$, or $-OR^a$;

R^a is, independently at each instance, H or C_{1-6} alkyl; and

R^b is, independently at each instance, C_{1-6} alkyl.

In another embodiment, in conjunction with any one of the above and
below embodiments, Q^1 is $C(R^5)$; Q^2 is $C(R^6)$; Q^3 is $C(R^7)$; and Q^4 is $C(R^6)$.

20 In another embodiment, in conjunction with any one of the above and
below embodiments, X^1 is NH.

In another embodiment, in conjunction with any one of the above and
below embodiments, X^1 is S.

25 In another embodiment, in conjunction with any one of the above and
below embodiments, X^1 is O.

In another embodiment, in conjunction with any one of the above and
below embodiments, X^2 is $C(R^8)$; and X^3 is $C(R^9)$.

In another embodiment, in conjunction with any one of the above and
below embodiments, X^2 is N; and X^3 is $C(R^9)$.

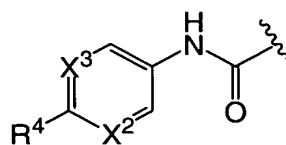
30 In another embodiment, in conjunction with any one of the above and
below embodiments, X^2 is $C(R^8)$; and X^3 is N.

In another embodiment, in conjunction with any one of the above and below embodiments, Y is NH.

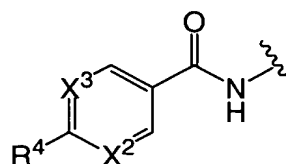
In another embodiment, in conjunction with any one of the above and below embodiments, Y is $C(R^{10})(R^{11})$.

5 In another embodiment, in conjunction with any one of the above and below embodiments, Y is CH_2 .

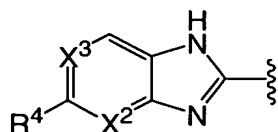
In another embodiment, in conjunction with any one of the above and below embodiments, R^1 is:



10 In another embodiment, in conjunction with any one of the above and below embodiments, R^1 is



In another embodiment, in conjunction with any one of the above and below embodiments, R^1 is



15

In another embodiment, in conjunction with any one of the above and below embodiments, R^2 is H or CH_3 .

In another embodiment, in conjunction with any one of the above and below embodiments, R^3 is Cl, Br, I, C_{1-6} alkyl, C_{1-4} haloalkyl or $-OC_{1-4}$ alkyl.

20 In another embodiment, in conjunction with any one of the above and below embodiments, R^4 is Br, I, C_{2-6} alkyl or C_{1-4} haloalkyl, wherein if Y is CH_2 and R^3 and R^5 are both Cl, then R^4 is other than isopropyl.

In another embodiment, in conjunction with any one of the above and below embodiments, R^4 is Br, I, t-butyl, isobutyl, n-butyl, sec-butyl, ethyl, n-propyl or C_{1-4} haloalkyl.

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In another embodiment, in conjunction with any one of the above and below embodiments, R⁶ is H.

In another embodiment, in conjunction with any one of the above and below embodiments, R⁷ is H.

5 In another embodiment, in conjunction with any one of the above and below embodiments, R⁸ is H.

In another embodiment, in conjunction with any one of the above and below embodiments, R⁸ is halo, C₁₋₆alkyl, C₁₋₄haloalkyl, -N(H)C₁₋₄alkyl, -N(C₁₋₄alkyl)C₁₋₄alkyl or -OC₁₋₄alkyl.

10 In another embodiment, in conjunction with any one of the above and below embodiments, R⁹ is H.

In another embodiment, in conjunction with any one of the above and below embodiments, R⁹ is halo, C₁₋₆alkyl, C₁₋₄haloalkyl, -N(H)C₁₋₄alkyl, -N(C₁₋₄alkyl)C₁₋₄alkyl or -OC₁₋₄alkyl.

15 In another embodiment, in conjunction with any one of the above and below embodiments, R¹⁰ is H; and R¹¹ is H.

Another aspect of the invention relates to a method of treating acute, inflammatory and neuropathic pain, dental pain, general headache, migraine, cluster headache, mixed-vascular and non-vascular syndromes, tension headache,
20 general inflammation, arthritis, rheumatic diseases, osteoarthritis, inflammatory bowel disorders, inflammatory eye disorders, inflammatory or unstable bladder disorders, psoriasis, skin complaints with inflammatory components, chronic inflammatory conditions, inflammatory pain and associated hyperalgesia and allodynia, neuropathic pain and associated hyperalgesia and allodynia, diabetic
25 neuropathy pain, causalgia, sympathetically maintained pain, deafferentation syndromes, asthma, epithelial tissue damage or dysfunction, herpes simplex, disturbances of visceral motility at respiratory, genitourinary, gastrointestinal or vascular regions, wounds, burns, allergic skin reactions, pruritus, vitiligo, general gastrointestinal disorders, gastric ulceration, duodenal ulcers, diarrhea, gastric
30 lesions induced by necrotising agents, hair growth, vasomotor or allergic rhinitis, bronchial disorders or bladder disorders, comprising the step of administering a compound according to any of the above embodiments.

Another aspect of the invention relates to a method of treating acute pain, comprising the step of administering a compound according to any of the above embodiments.

5 Another aspect of the invention relates to a method of treating inflammatory pain, comprising the step of administering a compound according to any of the above embodiments.

Another aspect of the invention relates to a method of treating neuropathic pain, comprising the step of administering a compound according to any of the above embodiments.

10 Another aspect of the invention relates to a pharmaceutical composition comprising a compound according to any of the above embodiments and a pharmaceutically-acceptable diluent or carrier.

Another aspect of the invention relates to the use of a compound according to any of the above embodiments as a medicament.

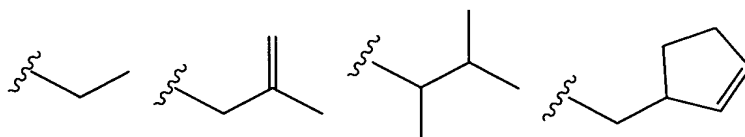
15 Another aspect of the invention relates to the use of a compound according to any of the above embodiments in the manufacture of a medicament for the treatment of acute, inflammatory and neuropathic pain, dental pain, general headache, migraine, cluster headache, mixed-vascular and non-vascular syndromes, tension headache, general inflammation, arthritis, rheumatic diseases,
20 osteoarthritis, inflammatory bowel disorders, inflammatory eye disorders, inflammatory or unstable bladder disorders, psoriasis, skin complaints with inflammatory components, chronic inflammatory conditions, inflammatory pain and associated hyperalgesia and allodynia, neuropathic pain and associated hyperalgesia and allodynia, diabetic neuropathy pain, causalgia, sympathetically
25 maintained pain, deafferentation syndromes, asthma, epithelial tissue damage or dysfunction, herpes simplex, disturbances of visceral motility at respiratory, genitourinary, gastrointestinal or vascular regions, wounds, burns, allergic skin reactions, pruritus, vitiligo, general gastrointestinal disorders, gastric ulceration, duodenal ulcers, diarrhea, gastric lesions induced by necrotising agents, hair
30 growth, vasomotor or allergic rhinitis, bronchial disorders or bladder disorders.

The compounds of this invention may have in general several asymmetric centers and are typically depicted in the form of racemic mixtures. This invention

is intended to encompass racemic mixtures, partially racemic mixtures and separate enantiomers and diastereomers.

Unless otherwise specified, the following definitions apply to terms found in the specification and claims:

- 5 "C_{α-β}alkyl" means an alkyl group comprising a minimum of α and a maximum of β carbon atoms in a branched, cyclical or linear relationship or any combination of the three, wherein α and β represent integers. The alkyl groups described in this section may also contain one or two double or triple bonds. Examples of C₁₋₆alkyl include, but are not limited to the following:

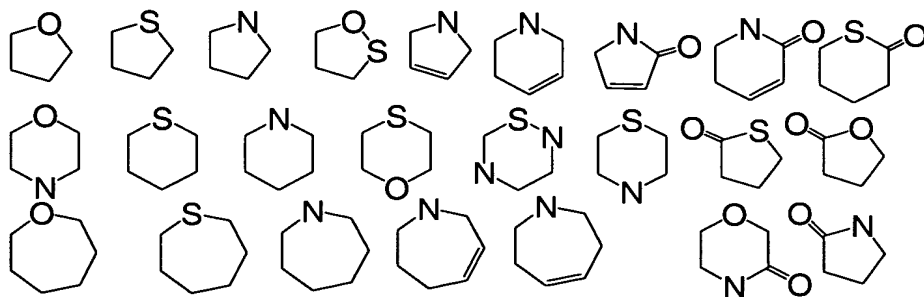


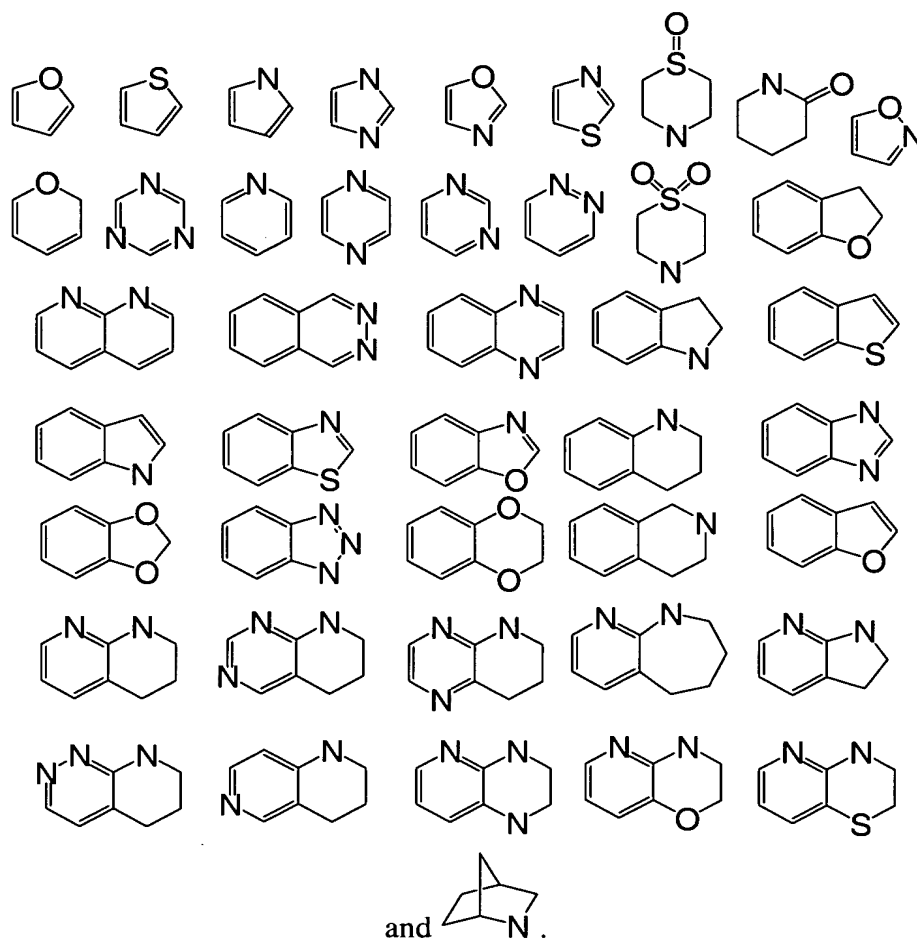
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"Benzo group", alone or in combination, means the divalent radical C₄H₄=, one representation of which is -CH=CH-CH=CH-, that when vicinally attached to another ring forms a benzene-like ring--for example tetrahydronaphthylene, indole and the like.

- 15 "Halo" or "halogen" means a halogen atoms selected from F, Cl, Br and I.
 "C_{α-β}haloalkyl" means an alkyl group, as described above, wherein any number--at least one--of the hydrogen atoms attached to the alkyl chain are replaced by F, Cl, Br or I.

- "Heterocycle" means a ring comprising at least one carbon atom and at least one other atom selected from N, O and S. Examples of heterocycles that may be found in the claims include, but are not limited to, the following:





5 “Available nitrogen atoms” are those nitrogen atoms that are part of a heterocycle and are joined by two single bonds (e.g. piperidine), leaving an external bond available for substitution by, for example, H or CH₃.

“Pharmaceutically-acceptable salt” means a salt prepared by conventional means, and are well known by those skilled in the art. The “pharmacologically

10 acceptable salts” include basic salts of inorganic and organic acids, including but not limited to hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulphonic acid, ethanesulfonic acid, malic acid, acetic acid, oxalic acid, tartaric acid, citric acid, lactic acid, fumaric acid, succinic acid, maleic acid, salicylic acid, benzoic acid, phenylacetic acid, mandelic acid and the like. When

15 compounds of the invention include an acidic function such as a carboxy group, then suitable pharmaceutically acceptable cation pairs for the carboxy group are well known to those skilled in the art and include alkaline, alkaline earth,

ammonium, quaternary ammonium cations and the like. For additional examples of "pharmacologically acceptable salts," *see infra* and Berge et al., J. Pharm. Sci. 66:1 (1977).

5 "Saturated or unsaturated" includes substituents saturated with hydrogens, substituents completely unsaturated with hydrogens and substituents partially saturated with hydrogens.

"Leaving group" generally refers to groups readily displaceable by a nucleophile, such as an amine, a thiol or an alcohol nucleophile. Such leaving groups are well known in the art. Examples of such leaving groups include, but are not limited to, 10 N-hydroxysuccinimide, N-hydroxybenzotriazole, halides, triflates, tosylates and the like. Preferred leaving groups are indicated herein where appropriate.

"Protecting group" generally refers to groups well known in the art which are used to prevent selected reactive groups, such as carboxy, amino, hydroxy, mercapto and the like, from undergoing undesired reactions, such as nucleophilic, electrophilic, 15 oxidation, reduction and the like. Preferred protecting groups are indicated herein where appropriate. Examples of amino protecting groups include, but are not limited to, aralkyl, substituted aralkyl, cycloalkenylalkyl and substituted cycloalkenyl alkyl, allyl, substituted allyl, acyl, alkoxycarbonyl, aralkoxycarbonyl, silyl and the like. Examples of aralkyl include, but are not limited to, benzyl, ortho- 20 methylbenzyl, trityl and benzhydryl, which can be optionally substituted with halogen, alkyl, alkoxy, hydroxy, nitro, acylamino, acyl and the like, and salts, such as phosphonium and ammonium salts. Examples of aryl groups include phenyl, naphthyl, indanyl, anthracenyl, 9-(9-phenylfluorenyl), phenanthrenyl, durenyl and the like. Examples of cycloalkenylalkyl or substituted cycloalkenylalkyl radicals, 25 preferably have 6-10 carbon atoms, include, but are not limited to, cyclohexenyl methyl and the like. Suitable acyl, alkoxycarbonyl and aralkoxycarbonyl groups include benzyloxycarbonyl, t-butoxycarbonyl, iso-butoxycarbonyl, benzoyl, substituted benzoyl, butyryl, acetyl, tri-fluoroacetyl, tri-chloro acetyl, phthaloyl and the like. A mixture of protecting groups can be used to protect the same amino 30 group, such as a primary amino group can be protected by both an aralkyl group and an aralkoxycarbonyl group. Amino protecting groups can also form a heterocyclic ring with the nitrogen to which they are attached, for example,

1,2-bis(methylene)benzene, phthalimidyl, succinimidyl, maleimidyl and the like and where these heterocyclic groups can further include adjoining aryl and cycloalkyl rings. In addition, the heterocyclic groups can be mono-, di- or tri-substituted, such as nitrophthalimidyl. Amino groups may also be protected against
5 undesired reactions, such as oxidation, through the formation of an addition salt, such as hydrochloride, toluenesulfonic acid, trifluoroacetic acid and the like. Many of the amino protecting groups are also suitable for protecting carboxy, hydroxy and mercapto groups. For example, aralkyl groups. Alkyl groups are also suitable groups for protecting hydroxy and mercapto groups, such as tert-butyl.

10 Silyl protecting groups are silicon atoms optionally substituted by one or more alkyl, aryl and aralkyl groups. Suitable silyl protecting groups include, but are not limited to, trimethylsilyl, triethylsilyl, tri-isopropylsilyl, tert-butyl dimethylsilyl, dimethylphenylsilyl, 1,2-bis(dimethylsilyl)benzene, 1,2-bis(dimethylsilyl)ethane and diphenylmethylsilyl. Silylation of an amino
15 groups provide mono- or di-silylamino groups. Silylation of aminoalcohol compounds can lead to a N,N,O-tri-silyl derivative. Removal of the silyl function from a silyl ether function is readily accomplished by treatment with, for example, a metal hydroxide or ammonium fluoride reagent, either as a discrete reaction step or in situ during a reaction with the alcohol group. Suitable
20 silylating agents are, for example, trimethylsilyl chloride, tert-butyl-dimethylsilyl chloride, phenyldimethylsilyl chloride, diphenylmethyl silyl chloride or their combination products with imidazole or DMF. Methods for silylation of amines and removal of silyl protecting groups are well known to those skilled in the art. Methods of preparation of these amine derivatives from corresponding amino
25 acids, amino acid amides or amino acid esters are also well known to those skilled in the art of organic chemistry including amino acid/amino acid ester or aminoalcohol chemistry.

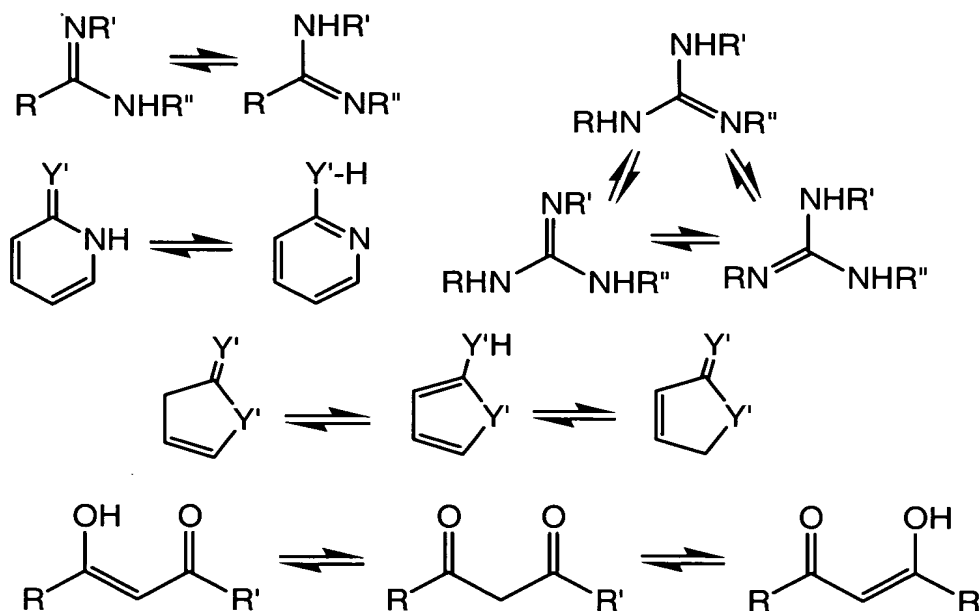
Protecting groups are removed under conditions which will not affect the remaining portion of the molecule. These methods are well known in the art and
30 include acid hydrolysis, hydrogenolysis and the like. A preferred method involves removal of a protecting group, such as removal of a benzyloxycarbonyl group by hydrogenolysis utilizing palladium on carbon in a suitable solvent

system such as an alcohol, acetic acid, and the like or mixtures thereof. A t-butoxycarbonyl protecting group can be removed utilizing an inorganic or organic acid, such as HCl or trifluoroacetic acid, in a suitable solvent system, such as dioxane or methylene chloride. The resulting amino salt can readily be

5 neutralized to yield the free amine. Carboxy protecting group, such as methyl, ethyl, benzyl, tert-butyl, 4-methoxyphenylmethyl and the like, can be removed under hydrolysis and hydrogenolysis conditions well known to those skilled in the art.

It should be noted that compounds of the invention may contain groups

10 that may exist in tautomeric forms, such as cyclic and acyclic amidine and guanidine groups, heteroatom substituted heteroaryl groups ($Y' = O, S, NR$), and the like, which are illustrated in the following examples:



and though one form is named, described, displayed and/or claimed herein, all the

15 tautomeric forms are intended to be inherently included in such name, description, display and/or claim.

Prodrugs of the compounds of this invention are also contemplated by this invention. A prodrug is an active or inactive compound that is modified

20 chemically through in vivo physiological action, such as hydrolysis, metabolism and the like, into a compound of this invention following administration of the prodrug to a patient. The suitability and techniques involved in making and using

prodrugs are well known by those skilled in the art. For a general discussion of prodrugs involving esters see Svensson and Tunek Drug Metabolism Reviews 165 (1988) and Bundgaard Design of Prodrugs, Elsevier (1985). Examples of a masked carboxylate anion include a variety of esters, such as alkyl (for example, methyl, ethyl), cycloalkyl (for example, cyclohexyl), aralkyl (for example, benzyl, p-methoxybenzyl), and alkylcarbonyloxyalkyl (for example, pivaloyloxymethyl). Amines have been masked as arylcarbonyloxymethyl substituted derivatives which are cleaved by esterases in vivo releasing the free drug and formaldehyde (Bungard J. Med. Chem. 2503 (1989)). Also, drugs containing an acidic NH group, such as imidazole, imide, indole and the like, have been masked with N-acyloxymethyl groups (Bundgaard Design of Prodrugs, Elsevier (1985)). Hydroxy groups have been masked as esters and ethers. EP 039,051 (Sloan and Little, 4/11/81) discloses Mannich-base hydroxamic acid prodrugs, their preparation and use.

The specification and claims contain listing of species using the language "selected from . . . and . . ." and "is . . . or . . ." (sometimes referred to as Markush groups). When this language is used in this application, unless otherwise stated it is meant to include the group as a whole, or any single members thereof, or any subgroups thereof. The use of this language is merely for shorthand purposes and is not meant in any way to limit the removal of individual elements or subgroups as needed.

Experimental

General

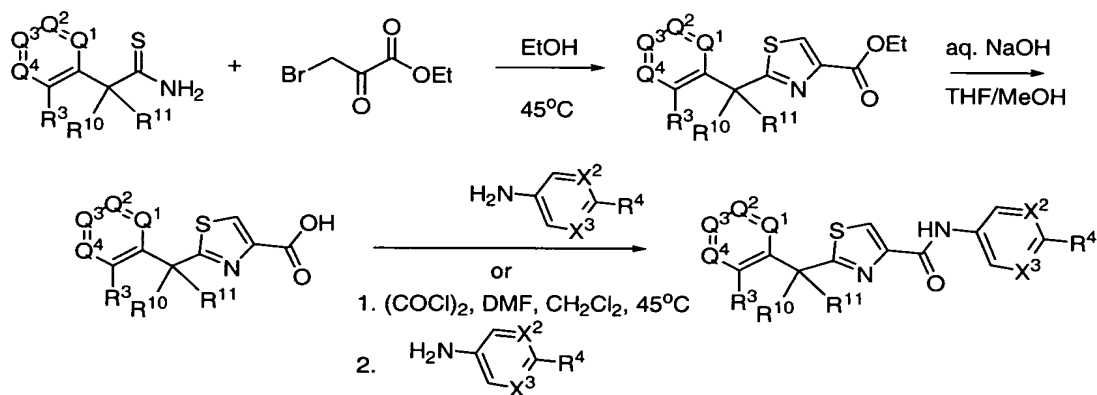
Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. All parts are by weight and temperatures are in degrees centigrade unless otherwise indicated. All compounds showed NMR spectra consistent with their assigned structures. Melting points were determined on a Buchi apparatus and are uncorrected. Mass spectral data was determined by electrospray ionization technique. All examples were purified to $\geq 95\%$ purity as determined by high-performance liquid chromatography. Unless otherwise stated, reactions were run at room temperature under a nitrogen atmosphere.

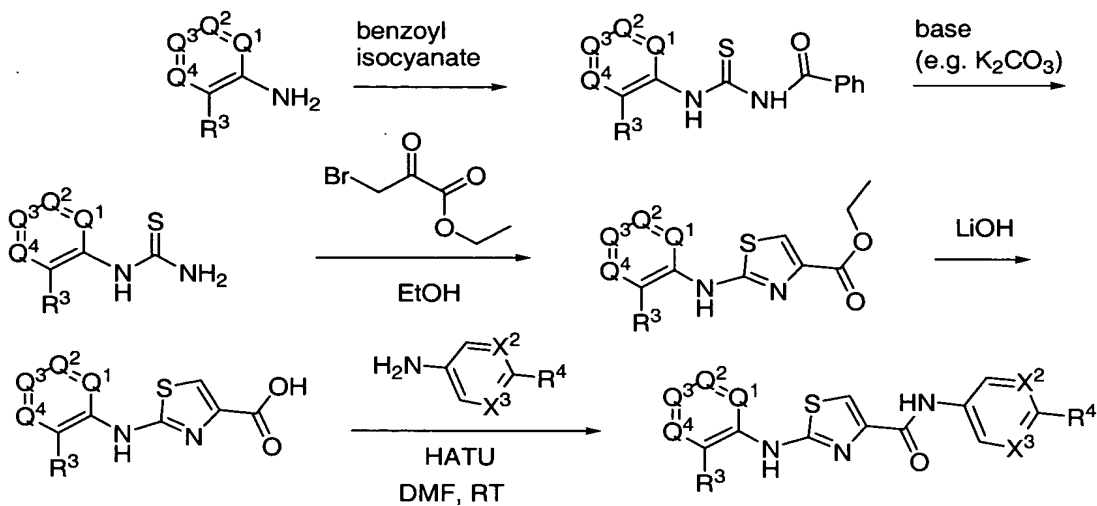
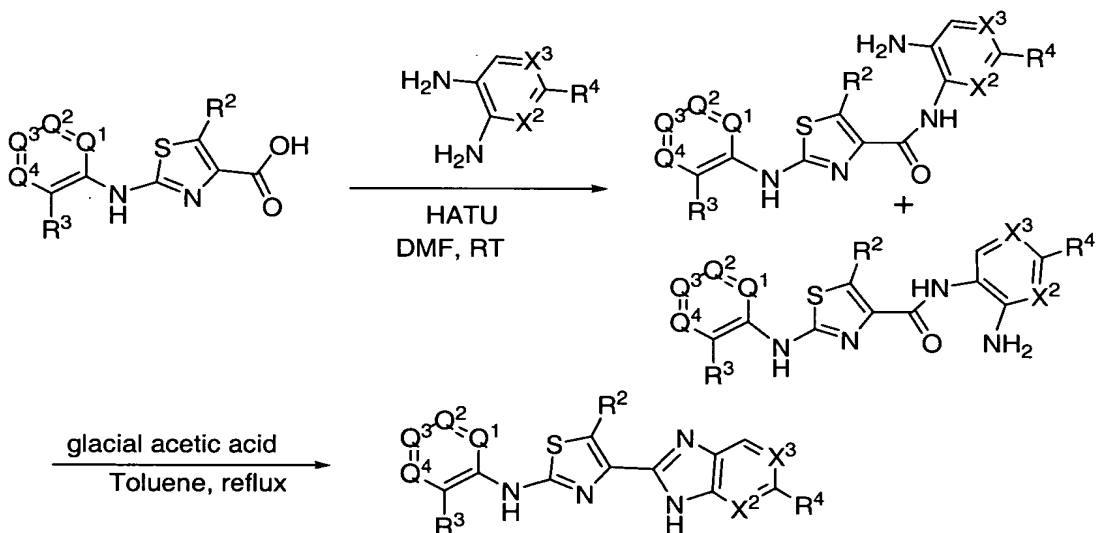
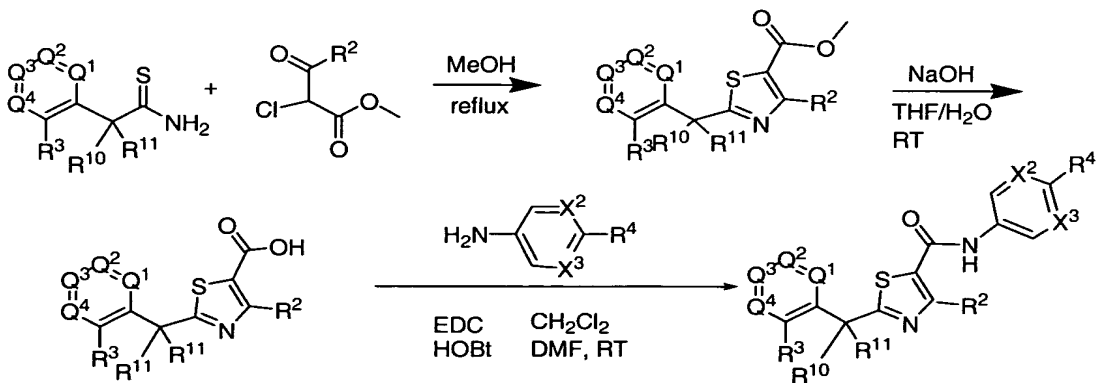
The following abbreviations are used:

	aq. -	aqueous
	BINAP -	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
	cond -	concentrated
5	DMF -	<i>N,N</i> -dimethylformamide
	Et ₂ O -	diethyl ether
	EtOAc -	ethyl acetate
	EtOH -	ethyl alcohol
	h -	hour
10	min -	minutes
	MeOH -	methyl alcohol
	satd -	saturated
	THF -	tetrahydrofuran

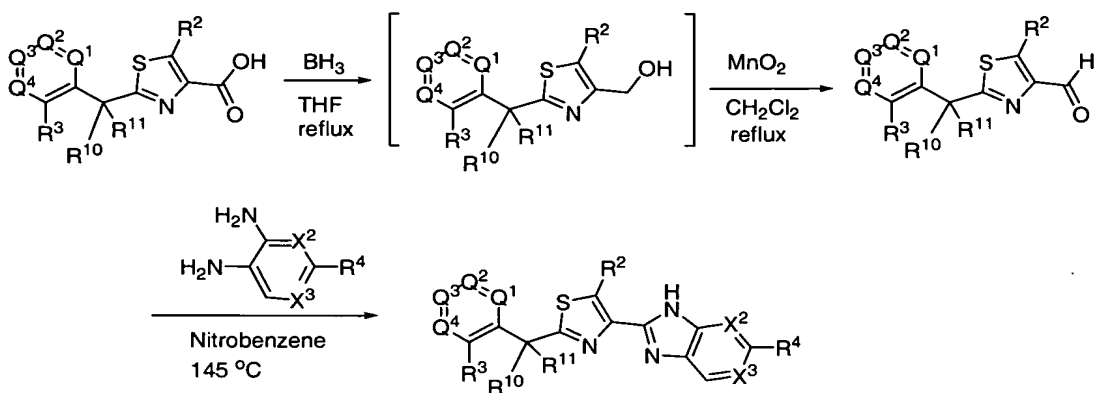
Generic Schemes for the preparation of compounds of the invention:

15 Scheme 1

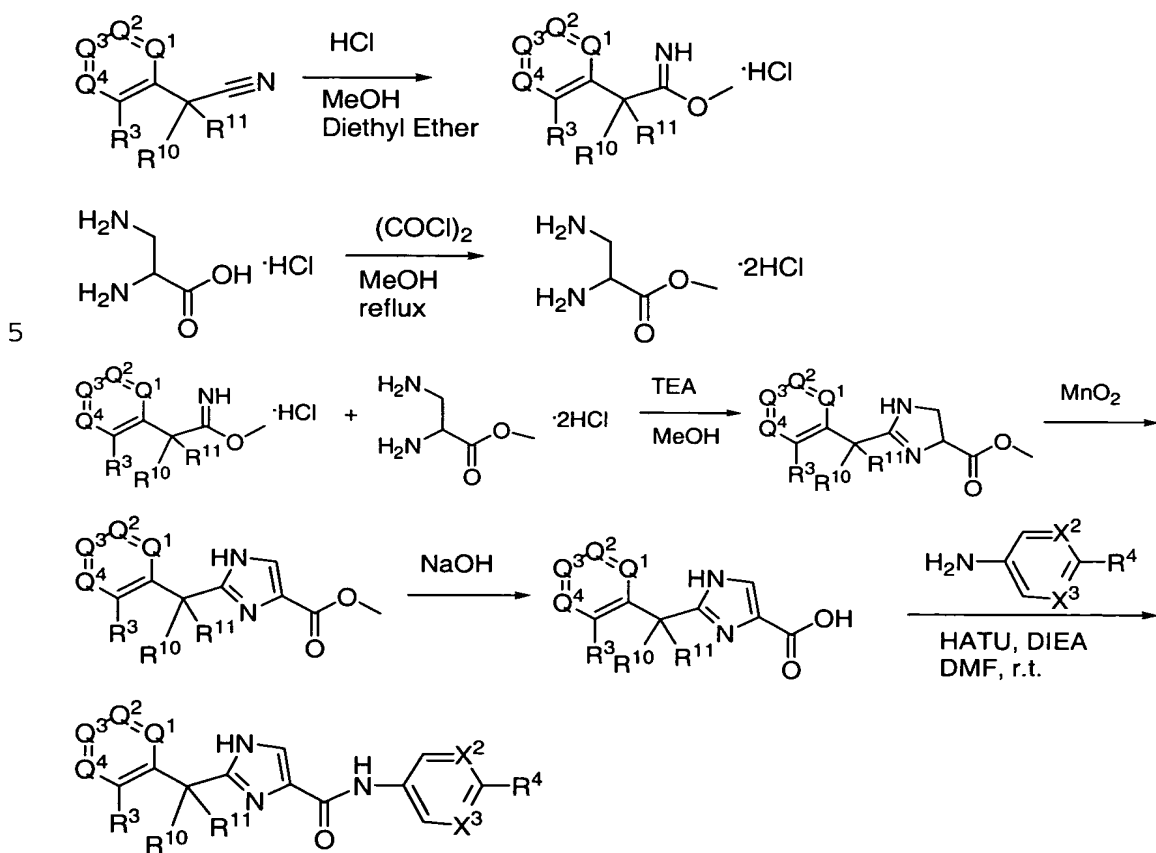


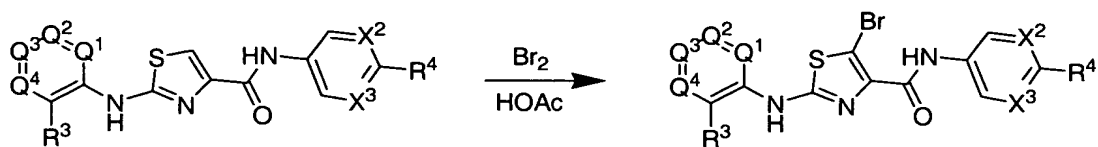
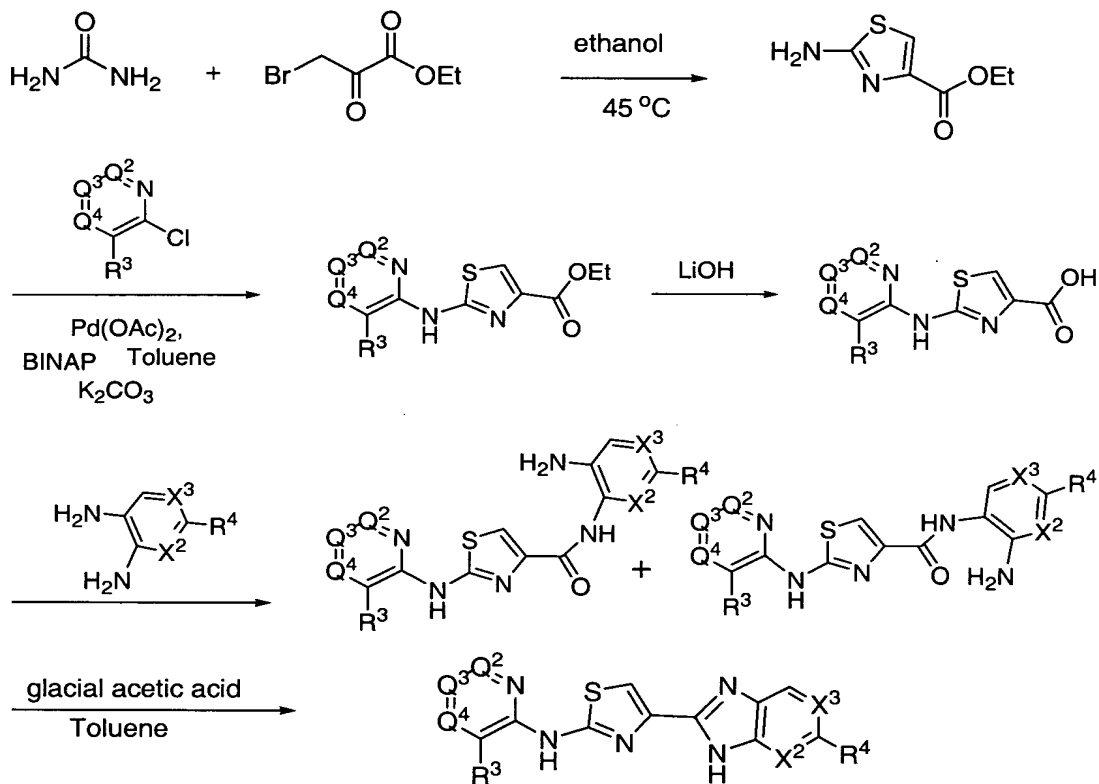
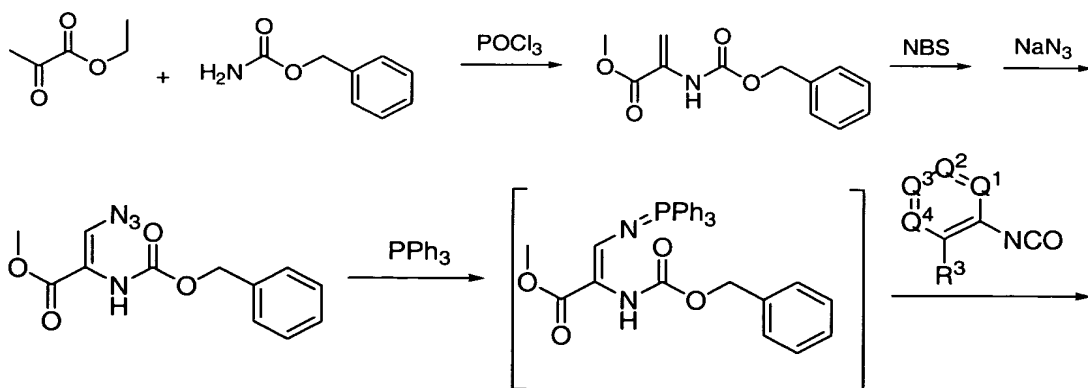
Scheme 2Scheme 35 Scheme 4

Scheme 5



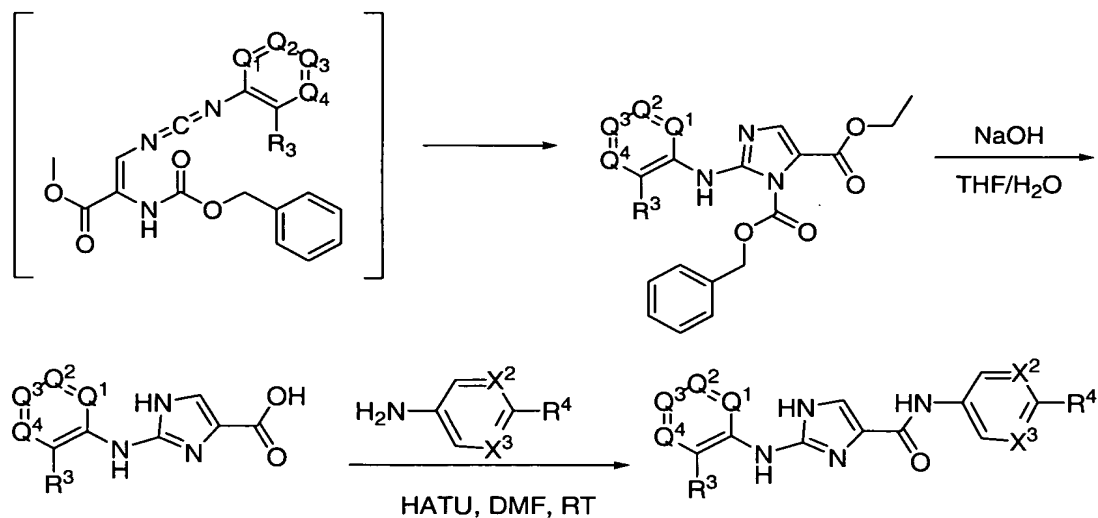
Scheme 6



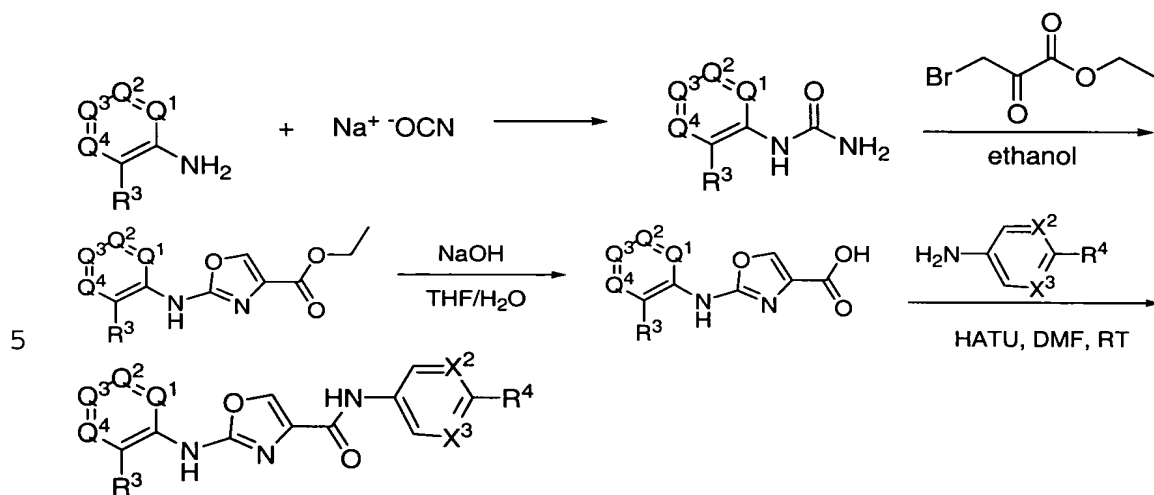
Scheme 7Scheme 8Scheme 9

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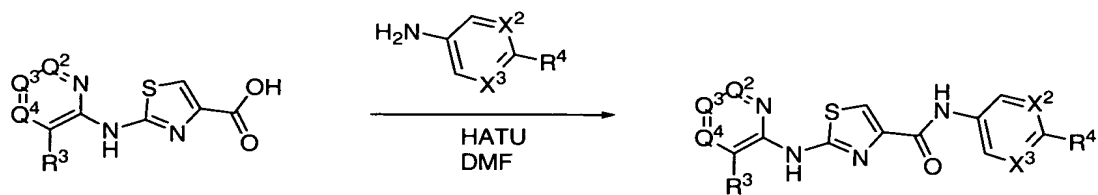
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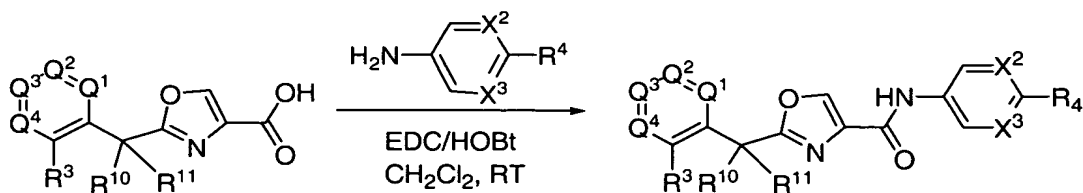
Scheme 10



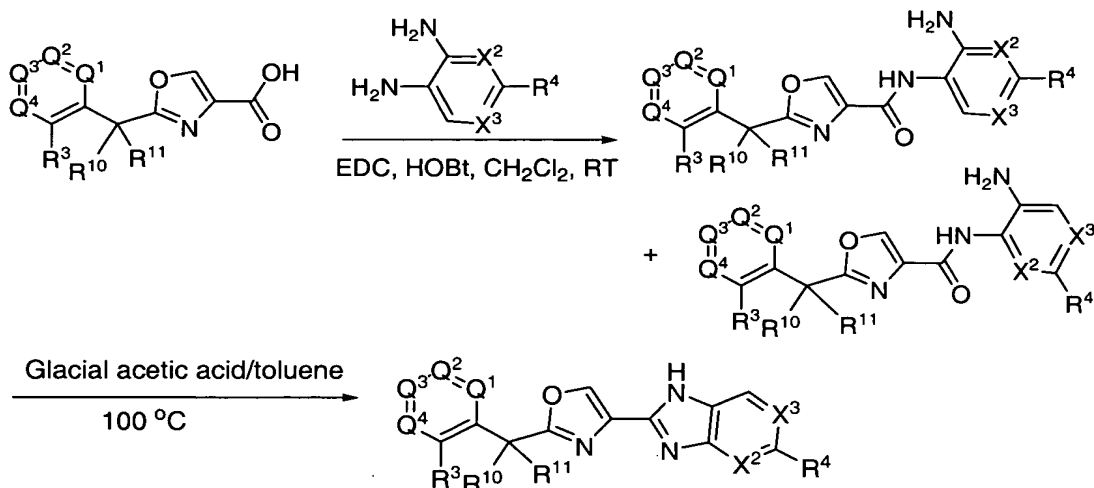
Scheme 11



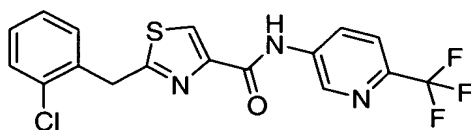
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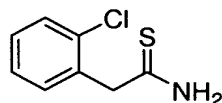
Scheme 15



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Example 1

{2-[(2-Chlorophenyl)methyl](1,3-thiazol-4-yl)}-N-[6-(trifluoromethyl)(3-pyridyl)]carboxamide.

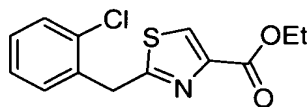


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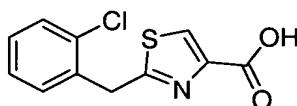
(a) 1-Amino-2-(2-chlorophenyl)ethane-1-thione. To a 100-mL round-bottomed flask was added 2-chlorobenzyl cyanide (4.53 g, 30 mmol, Aldrich), pyridine (30 mL, Aldrich) and trimethyl amine (12 mL, 90 mmol, Aldrich). Hydrogen sulfide (Aldrich) was bubbled through the reaction solution at 0 °C for 1 h. After the reaction mixture was stirred at room temperature overnight, nitrogen was bubbled through the reaction solution for 15 min at room temperature. Solvent was removed in vacuo. The residue was diluted in 100 mL of EtOAc, and washed with 2% aqueous HCl (50 mL) and brine (100 mL). The organic phase was dried

15

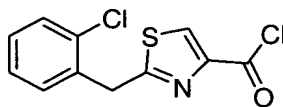
over anhydrous MgSO_4 , filtered and concentrated in vacuo to give the title product as a crude yellow solid. MS (ESI, pos. ion) m/z : 186 ($M+1$); MS (ESI, neg. ion) m/z : 184 ($M-1$).



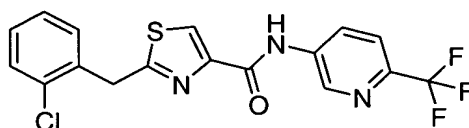
- 5 (b) Ethyl 2-[(2-chlorophenyl)methyl]-1,3-thiazole-4-carboxylate. To a 100-mL, round-bottomed flask was added 1-amino-2-(2-chlorophenyl)ethane-1-thione (1.85 g, 10 mmol), pyridine (2.4 mL, 30 mmol, Aldrich), ethyl bromopyruvate (1.94 g, 10 mmol, Aldrich) and ethyl alcohol (35 mL). The reaction solution was heated at reflux overnight. After the solvent was removed in *vacuo*, the residue
- 10 was diluted with 200 mL of EtOAc and a white precipitate was filtered. The filtrate was washed with saturated aqueous NaHCO_3 (150 mL) and brine (150 mL). The separated organic phase was dried over anhydrous MgSO_4 , filtered, and concentrated in vacuo. Purification by silica gel column chromatography (hexane/EtOAc, 4:1) provided the title compound as a white solid. MS (ESI, pos.
- 15 ion) m/z : 282 ($M+1$); MS (ESI, neg. ion) m/z : 280 ($M-1$).



- (c) 2-[(2-Chlorophenyl)methyl]-1,3-thiazole-4-carboxylic acid. To a 50-mL, round bottomed flask was added ethyl 2-[(2-chlorophenyl)methyl]-1,3-thiazole-4-carboxylate (2.81 g, 10 mmol), THF (15 mL, Aldrich), methyl alcohol (10 mL)
- 20 and aqueous NaOH (5 N, 10 mL, 50 mmol, J.T. Baker). The reaction solution was stirred at room temperature overnight. The organic solvent was removed in vacuo, and the residue was diluted with H_2O (20 mL) and cooled to 0 °C. Aqueous HCl (10 %) was added to the aqueous phase and the acidity of the aqueous phase was adjusted to $\text{pH} < 4$ (monitored by pH paper). Filtration of the
- 25 precipitate from the aqueous phase provided the title product as a white solid. MS (ESI, pos. ion) m/z : 254 ($M+1$); MS (ESI, neg. ion) m/z : 252 ($M-1$).

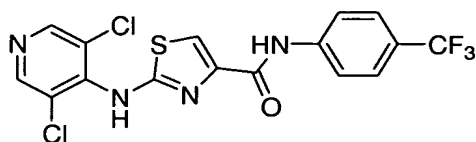


- (d) 2-(2-Chloro-benzyl)-thiazole-4-carbonyl chloride. To a 100-mL, round-bottomed flask was added 2-[(2-chlorophenyl)methyl]-1,3-thiazole-4-carboxylic acid (2.31 g, 9.1 mmol), CH₂Cl₂ (60 mL), oxalyl chloride (5.8 g, 45 mmol, Aldrich) and DMF (0.1 mL, Aldrich). The reaction solution was stirred at room temperature for 6 h. The volatile portion was removed in *vacuo*. The title compound was obtained as a yellow solid. MS (ESI, pos. ion) *m/z*: 272 (M+1); MS (ESI, neg. ion) *m/z*: 270 (M-1).

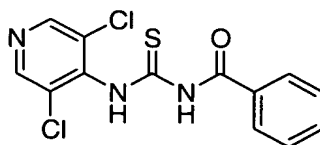


- (e) {2-[(2-Chlorophenyl)methyl](1,3-thiazol-4-yl)}-N-[6-(trifluoromethyl)(3-pyridyl)]carboxamide. To a 50-mL, round-bottomed flask was added 3-amino-6-(trifluoromethyl)pyridine (0.09 g, 0.55 mmol, Matrix Scientific), K₂CO₃ powder (0.23 g, 1.66 mmol, Sigma-Aldrich Chemicals), CH₂Cl₂ (2mL), and 2-(2-chloro-benzyl)-thiazole-4-carbonyl chloride (0.15 g, 0.55 mmol). The mixture was stirred at room temperature overnight. The solid was filtered and washed with CH₂Cl₂. The solution was washed with H₂O (2 x), and brine, dried over Na₂SO₄, filtered and concentrated in *vacuo*. Purification by silica gel chromatography (10%-15% EtOAc in hexane) provided the title compound as a white solid. MS (ESI, pos. ion) *m/z*: 396, 398 (M+1). MP: 99-101 °C.

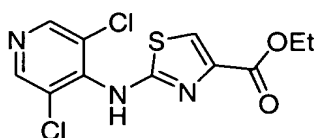
20 Example 2



{2-[(3,5-Dichloro(4-pyridyl))amino](1,3-thiazol-4-yl)}-N-[4-(trifluoromethyl)-phenyl]carboxamide.

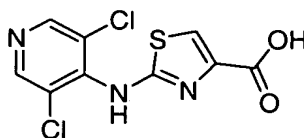


- (a) N-[(3,5-Dichloro(4-pyridyl))amino]thioxomethylbenzamide. To a 500-mL, round-bottomed flask was added 4-amino-3,5-dichloropyridine (5.0 g, 31 mmol, Lancaster), benzoyl isothiocyanate (5.0 g, 31 mmol, Aldrich) and CHCl_3 (250 mL).
5 The reaction solution was stirred at 60 °C for 72 h. The reaction solution was allowed to cool to room temperature and concentrated in vacuo. Purification by silica gel column chromatography (hexane/EtOAc, 5:1) provided the title compound as a yellow solid. MS (ESI, pos. ion) m/z : 327 (M+1); MS (ESI, neg. ion) m/z : 325 (M-1).

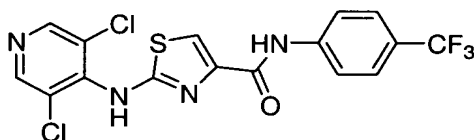


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- (b) Ethyl 2-[(3,5-dichloro-4-pyridyl)amino]-1,3-thiazole-4-carboxylate. To a 500-mL, round-bottomed flask was added N-[(3,5-dichloro(4-pyridyl))amino]thioxomethylbenzamide (6.26 g, 19 mmol), K_2CO_3 (2.9 g, 21 mmol, Aldrich), ethyl alcohol (150 mL, Aldrich) and water (50 mL). The reaction mixture was stirred at
15 80 °C for 16 h and then it was allowed to cool to room temperature. Ethyl bromopyruvate (4.1 g, 21 mmol, Aldrich) was added to the reaction mixture. The reaction solution was stirred at 60 °C for an additional 6 h. After cooling to room temperature, the reaction mixture was filtered, and ethyl alcohol was removed from the filtrate in vacuo. The resultant aqueous phase was extracted with EtOAc
20 (4 x 50 mL). The combined organic layers were washed with satd aqueous NaHCO_3 (150 mL), brine (150 mL), dried over anhydrous MgSO_4 and concentrated in vacuo. Purification by silica gel column chromatography (hexane/EtOAc, 5:2) provided the title compound as a light-yellow solid. MS (ESI, pos. ion) m/z : 318 (M+1); MS (ESI, neg. ion) m/z : 316 (M-1).

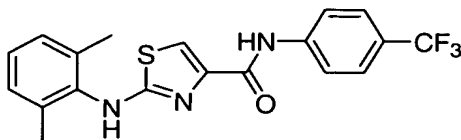


(c) 2-[(3,5-Dichloro-4-pyridyl)amino]-1,3-thiazole-4-carboxylic acid. According to the procedure described in step (c) of **Example 1**, the title product was obtained from ethyl 2-[(3,5-dichloro-4-pyridyl)amino]-1,3-thiazole-4-carboxylate (3.1 g, 10 mmol), 5 N aqueous NaOH (6 mL, 30 mmol, J.T. Baker), MeOH (30 mL, Aldrich) and THF (50 mL, Aldrich) as white solid. MS (ESI, pos. ion) m/z: 290 (M+1); MS (ESI, neg. ion) m/z: 288 (M-1).

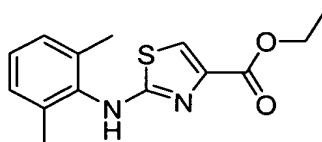


(d) {2-[(3,5-Dichloro(4-pyridyl))amino](1,3-thiazol-4-yl)}-N-[4-(trifluoromethyl)phenyl]carboxamide. To a 25-mL, round-bottomed flask was added 2-[(3,5-dichloro-4-pyridyl)amino]-1,3-thiazole-4-carboxylic acid (289 mg, 1.0 mmol), 4-aminobenzotrifluoride (161 mg, 1.0 mmol, Aldrich), HATU:[o-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate] (456 mg, 1.2 mmol, Perseptive Biosystems), DIEA (156 mg, 1.2 mmol, Aldrich) and DMF (8 mL). The reaction solution was allowed to stir at room temperature overnight. The solvent was removed in vacuo, and the residue was diluted in EtOAc (50 mL) and washed with satd aqueous NaHCO₃ (50 mL) and brine (50 mL). The resultant organic phase was dried over anhydrous MgSO₄ and concentrated in vacuo. Purification by silica gel column chromatography (hexane/ EtOAc, 7:2) provided the title compound as a white solid. MS (ESI, pos. ion) m/z: 433 (M+1); MS (ESI, neg. ion) m/z: 431 (M-1). MP: 195-197 °C.

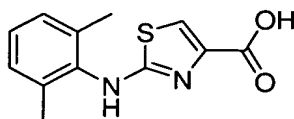
Example 3



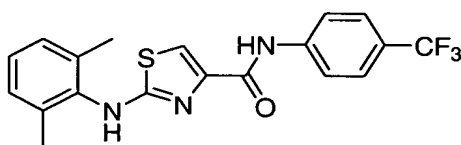
{2-[(2,6-Dimethylphenyl)amino](1,3-thiazol-4-yl)}-N-[4-(trifluoromethyl)phenyl]carboxamide.



- (a) Ethyl 2-[(2,6-dimethylphenyl)amino]-1,3-thiazole-4-carboxylate. To a round-bottomed flask were added 1-(2,6-dimethylphenyl)-2-thiourea (3.0 g, 16.6 mmol, Transworld Chemicals), ethyl bromopyruvate (2.1 mL, 16.6 mmol, Aldrich) and EtOH (40 mL). The reaction mixture was stirred at 60 °C overnight. Solvent was removed in vacuo. Purification by silica gel chromatography (gradient: 0-50% EtOAc in hexane, followed by 0-10% MeOH in CH₂Cl₂) provided the title compound as a white solid. MS (ESI, pos. ion) *m/z*: 277 (M+1).



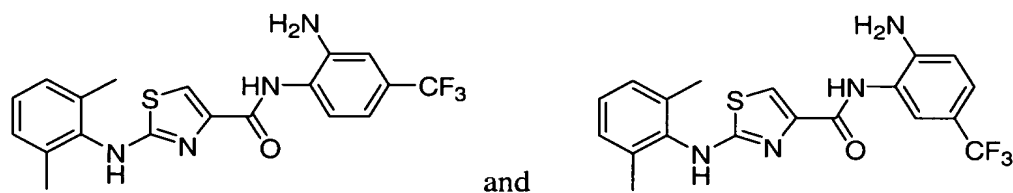
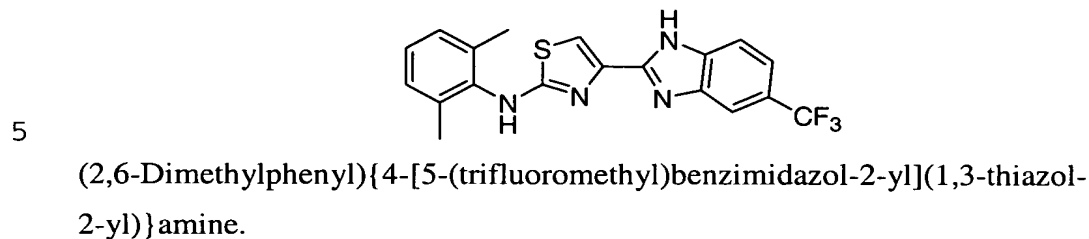
- (b) 2-[(2,6-Dimethylphenyl)amino]-1,3-thiazole-4-carboxylic acid. To a round-bottomed flask were added ethyl 2-[(2,6-dimethylphenyl)amino]-1,3-thiazole-4-carboxylate (3.29 g, 11.9 mmol), LiOH monohydrate (2.5 g, 59.6 mmol, Aldrich) and wet EtOH (60 mL). The reaction mixture was stirred at room temperature for 3 d, and neutralized with aqueous HCl (2.0 M, 30 mL). After removal of the EtOH in vacuo, the aqueous phase was extracted with EtOAc (3 x 80 mL). The combined organic extracts were washed with satd NaCl solution, dried over Na₂SO₄, filtered and concentrated in vacuo. The title compound was obtained as a white solid. MS (ESI, pos. ion) *m/z*: 249 (M+1).



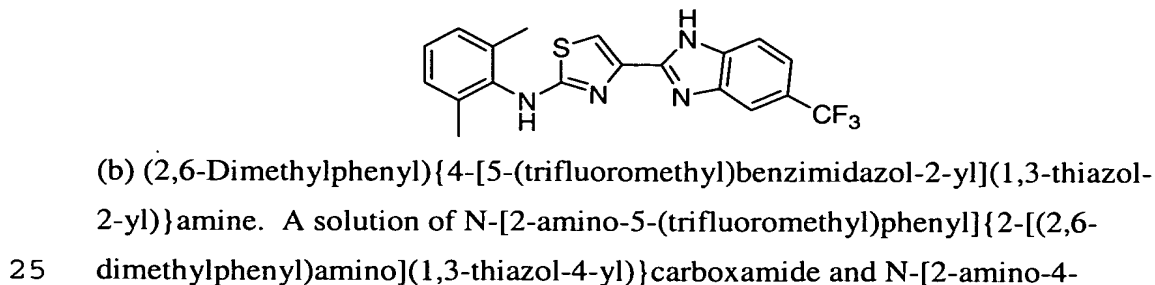
- (c) {2-[(2,6-Dimethylphenyl)amino](1,3-thiazol-4-yl)}-N-[4-(trifluoromethyl)phenyl]carboxamide. To a round-bottomed flask was added 2-[(2,6-dimethylphenyl)amino]-1,3-thiazole-4-carboxylic acid (300 mg, 1.21 mmol), 4-trifluoromethylaniline (0.137 mL, 1.09 mmol, Aldrich) and HATU:[o-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate] (690 mg, 1.82 mmol, Perseptive Biosystems) and DMF (2.0 mL). The reaction mixture was stirred at room temperature for 88 h. After removal of DMF, purification by silica

gel chromatography (gradient: 0-8% EtOAc in hexane) provided the title compound as a light yellow solid. MS (ESI, pos. ion) m/z : 392 (M+1). MP: 216 – 218 °C.

Example 4

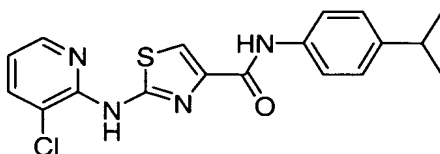


(a) N-[2-Amino-5-(trifluoromethyl)phenyl]{2-[(2,6-dimethylphenyl)amino](1,3-thiazol-4-yl)}carboxamide and N-[2-amino-4-(trifluoromethyl)phenyl]{2-[(2,6-dimethylphenyl)amino](1,3-thiazol-4-yl)}carboxamide. To a round-bottomed flask were added 2-[(2,6-dimethylphenyl)amino]-1,3-thiazole-4-carboxylic acid (777 mg, 3.1 mmol), 4-(trifluoromethyl)-1,2-phenylenediamine (551 mg, 3.1 mmol, Lancaster), HATU:[o-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate] (1.79 g, 4.7 mmol, Perseptive Biosystems) and DMF (5 mL). The reaction mixture was stirred at room temperature for 5 d. After removal of DMF, the crude product was diluted with H₂O (80 mL), and extracted with CH₂Cl₂ (3 x 80 mL). The combined organic phase was washed with satd NaCl, dried over Na₂SO₄, filtered and concentrated in vacuo. Purification by silica gel chromatography (0-28% EtOAc in hexane) provided the title compounds as a brown solid. MS (ESI, pos. ion) m/z : 407 (M+1).

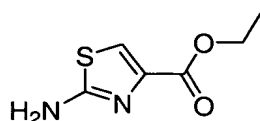


(trifluoromethyl)phenyl]{2-[(2,6-dimethylphenyl)amino](1,3-thiazol-4-yl)}carboxamide (200 mg, 0.49 mmol) in glacial acetic acid (4 mL) and toluene (4 mL) was stirred at 100 °C for 2 h. Solvents were removed in vacuo. Purification by silica gel chromatography (gradient: 0-30% EtOAc in hexane) provided the
 5 title compound as an off-white solid. MS (ESI, pos. ion) m/z : 389 (M+1). MP: 250 – 251 °C.

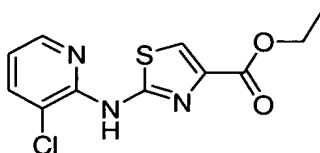
Example 5



10 {2-[(3-Chloro(2-pyridyl))amino](1,3-thiazol-4-yl)}-N-[4-(methylethyl)phenyl]-carboxamide.

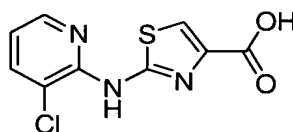


(a) Ethyl 2-amino-1,3-thiazole-4-carboxylate. To a round-bottomed flask were added thiourea (5.0 g, 65.7 mmol, Aldrich), EtOH (150 mL) and ethyl bromopyruvate (9.2 mL, 65.7 mmol, Aldrich). The reaction mixture was stirred at 45 °C
 15 for 18 h. EtOH was removed in vacuo. The crude product was diluted with satd NaHCO₃ (100 mL) and H₂O (100 mL). The aqueous phase was extracted with EtOAc (3 x 200 mL). The combined organic extracts were washed with satd NaCl (200 mL), dried over Na₂SO₄, filtered and concentrated in vacuo. Crystallization in EtOAc-MeOH provided the title compound as a yellow crystalline solid. MS
 20 (ESI, pos. ion) m/z : 173 (M+1).

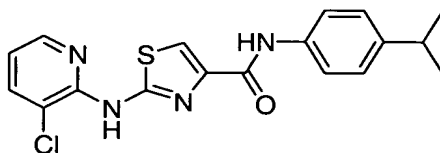


(b) Ethyl 2-[(3-chloro-2-pyridyl)amino]-1,3-thiazole-4-carboxylate. A mixture of ethyl 2-amino-1,3-thiazole-4-carboxylate (2.33 g, 13.5 mmol), 2,3-dichloropyridine (2.0 g, 13.5 mmol, Lancaster), palladium (II) acetate (152 mg, 0.68
 25 mmol, Strem Chemicals), *rac*-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (420 mg, 0.68 mmol, Aldrich), potassium carbonate (37.3 g, Mallinckrodt) and toluene

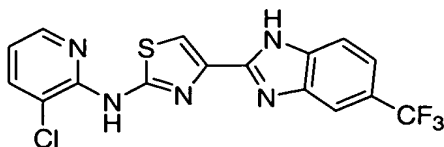
(55 mL) in a sealed flask was stirred at 112 °C under N₂ for 2 d. The reaction mixture was passed through a pad of Celite and the Celite pad was washed with EtOAc (5 x 100 mL). The organic layer was diluted with H₂O (200 mL), and separated from the aqueous phase. The aqueous phase was extracted with EtOAc (150 mL). The combined organic phase was washed with satd NaCl (200 mL), dried over Na₂SO₄, filtered and concentrated in vacuo. Purification by silica gel chromatography (0-15% EtOAc in hexane) provided the title compound as a white solid. MS (ESI, pos. ion) *m/z*: 284 (M+1).



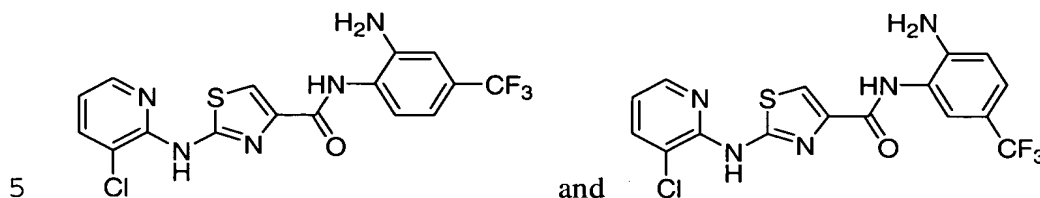
(c) 2-[(3-Chloro-2-pyridyl)amino]-1,3-thiazole-4-carboxylic acid. A mixture of ethyl 2-[(3-chloro-2-pyridyl)amino]-1,3-thiazole-4-carboxylate (1.42 g, 5.02 mmol) and LiOH (361 mg, 15.1 mmol, Aldrich) in 95% EtOH (20 mL) was stirred at room temperature for 5 h. The reaction mixture was neutralized with aqueous HCl (2.0 M, 7.5 mL, 15.0 mmol) and concentrated under reduced pressure. The material was dried in vacuo overnight to provide the title product as a white solid, which contained LiCl as a byproduct. MS (ESI, pos. ion) *m/z*: 256 (M+1).



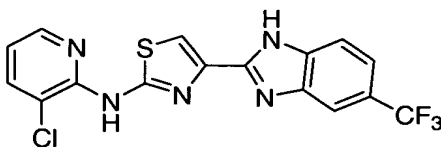
(d) {2-[(3-Chloro(2-pyridyl))amino](1,3-thiazol-4-yl)}-N-[4-(methylethyl)phenyl]carboxamide. A mixture of 2-[(3-chloro-2-pyridyl)amino]-1,3-thiazole-4-carboxylic acid (280 mg, the crude product from step (c) above), 4-isopropylaniline (0.095 mL, 0.69 mmol) and HATU :[o-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate] (416 mg, 1.10 mmol, Perseptive Biosystems) in DMF (3.0 mL) was stirred at room temperature overnight. After removal of DMF, purification by silica gel chromatography (gradient: 0-15% EtOAc in hexane) provided the title compound as a white solid. MS (ESI, pos. ion) *m/z*: 373 (M+1).

Example 6

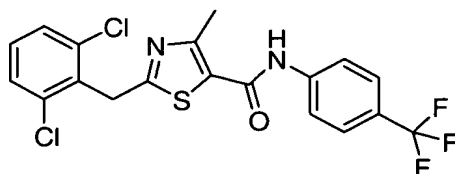
(3-Chloro(2-pyridyl)){4-[5-(trifluoromethyl)benzimidazol-2-yl](1,3-thiazol-2-yl)}amine.



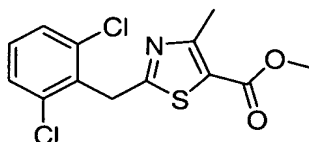
(a) N-[2-Amino-5-(trifluoromethyl)phenyl]{2-[(3-chloro(2-pyridyl))amino](1,3-thiazol-4-yl)}carboxamide and N-[2-amino-4-(trifluoromethyl)phenyl]{2-[(3-chloro(2-pyridyl))amino](1,3-thiazol-4-yl)}carboxamide. A solution of 2-[(3-chloro-2-pyridyl)amino]-1,3-thiazole-4-carboxylic acid (573 mg), 4-
 10 (trifluoromethyl)-1,2-phenylenediamine (264 mg, 1.50 mmol, Lancaster) and HATU :[o-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate] (855 mg, 2.25 mmol, Perseptive Biosystems) in DMF (5 mL) was stirred at room temperature for 6 d. After the removal of DMF, purification by silica gel chromatography (0-25% EtOAc in hexane) provided the
 15 title compounds as a brown solid. MS (ESI, pos. ion) *m/z*: 414 (M+1).



(b) (3-Chloro(2-pyridyl)){4-[5-(trifluoromethyl)benzimidazol-2-yl](1,3-thiazol-2-yl)}amine. A solution of N-[2-amino-5-(trifluoromethyl)phenyl]{2-[(3-chloro(2-pyridyl))amino](1,3-thiazol-4-yl)}carboxamide and N-[2-amino-4-
 20 (trifluoromethyl)phenyl]{2-[(3-chloro(2-pyridyl))amino](1,3-thiazol-4-yl)}carboxamide (62 mg, 0.15 mmol) in glacial acetic acid (2.5 mL) and toluene (2 mL) was stirred at 100 °C for 2.5 h. Solvents were removed in vacuo. Purification by silica gel chromatography (0-2% MeOH in CH₂Cl₂) provided the title compound as a brown solid. MS (ESI, pos. ion) *m/z*: 396 (M+1). MP: 207 –
 25 208 °C.

Example 7

{2-[(2,6-Dichlorophenyl)methyl]-4-methyl(1,3-thiazol-5-yl)}-N-[4-(trifluoromethyl)phenyl]carboxamide.

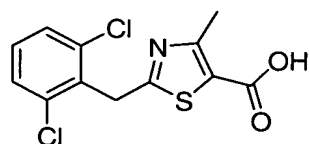


5

(a) Methyl 2-[(2,6-dichlorophenyl)methyl]-4-methyl-1,3-thiazole-5-carboxylate.

To a round-bottomed flask charged with 2-(2,6-dichlorophenyl)ethanethioamide (1.00 g, 4.54 mmol, Maybridge), was added MeOH (10 mL), and methyl 2-chloro-acetoacetate (0.55 mL, 4.54 mmol, Aldrich). The solution was stirred at 60 °C for 2 d, and concentrated in vacuo. Purification by silica gel chromatography (3%-10% EtOAc in hexane) provided the title product as a white solid. MS (ESI, pos. ion) m/z : 316 (M+1).

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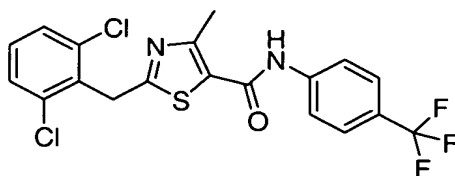


(b) 2-[(2,6-Dichlorophenyl)methyl]-4-methyl-1,3-thiazole-5-carboxylic acid. To

15

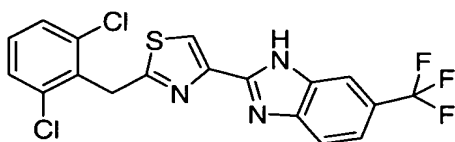
a round-bottomed flask containing methyl 2-[(2,6-dichlorophenyl)methyl]-4-methyl-1,3-thiazole-5-carboxylate (1.15 g, 3.65 mmol) was added THF (6 mL), solid NaOH (0.58 g, 14.6 mmol), and H₂O (6 mL). The mixture was stirred at room temperature overnight, and KOH (0.82 g, 14.60 mmol) was added. The mixture was stirred at room temperature for 3 h, concentrated in vacuo and acidified with 1 N HCl to pH ~4-5. The white solid was filtered and dried to afford the title product. MS (ESI, pos. ion) m/z : 302 (M+1).

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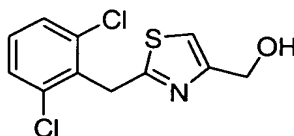


(c) {2-[(2,6-Dichlorophenyl)methyl]-4-methyl(1,3-thiazol-5-yl)}-N-[4-(trifluoromethyl)phenyl]carboxamide. To a 25-mL, round-bottomed flask was added 2-[(2,6-dichlorophenyl)methyl]-4-methyl-1,3-thiazole-5-carboxylic acid (150 mg, 0.50 mmol), 4-(trifluoromethyl)aniline (80 mg, 0.50 mmol, Aldrich), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (143 mg, 0.75 mmol, Aldrich), 1-hydroxybenzotriazole (67 mg, 0.50 mmol, Aldrich), DMF (1.0 mL), and CH₂Cl₂ (1.5 mL). The reaction mixture was stirred at room temperature overnight and diluted with CH₂Cl₂ (50 mL). The organic phase was washed with Na₂CO₃ (2 x) and brine, dried over Na₂SO₄, filtered and concentrated to afford a yellow solid. Purification by silica gel chromatography (10% EtOAc in hexane), followed by Prep HPLC (5%-95% CH₃CN/H₂O), provided the title product as a white solid. MS (ESI, pos. ion) *m/z*: 445 (M+1). MP: 180-183 °C.

Example 8

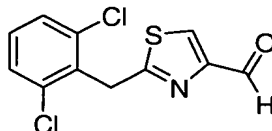


2-[(2,6-Dichlorophenyl)methyl]-4-[6-(trifluoromethyl)benzimidazol-2-yl]-1,3-thiazole.

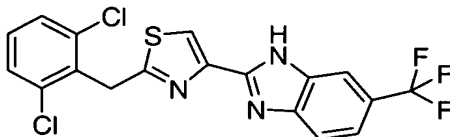


(a) {2-[(2,6-Dichlorophenyl)methyl]-1,3-thiazol-4-yl}methan-1-ol. To a 100-mL, round-bottomed flask equipped with condenser was added 2-[(2,6-dichlorophenyl)methyl]-1,3-thiazole-4-carboxylic acid, Example 9(c), (1.5 g, 5.2 mmol), THF (7 mL), and BH₃ (1.0 M solution in THF, 10.4 mL, 10.4 mmol, Aldrich). The reaction mixture was heated at reflux for 6 h, and then allowed to cool to room temperature. The reaction mixture was allowed to stand at room temperature for 2 d, and was heated at reflux for additional 4 h. The mixture was

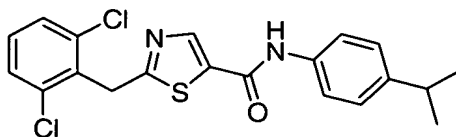
cooled to room temperature and the resultant suspension was filtered. The filtrate was cooled in an ice-bath and diluted with MeOH. The methanolic solution was evaporated under reduced pressure and the residue was dried in vacuo to give the title compound as a white solid. The crude product was used in next step without further purification. MS (ESI, pos. ion) m/z : 274 (M+1).



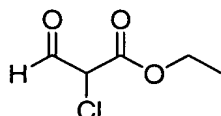
(b) {2-[(2,6-Dichlorophenyl)methyl]-1,3-thiazol-4-yl} formaldehyde. To a 150-mL, round-bottomed flask was added CH_2Cl_2 (20 mL), MnO_2 (5.6 g, 58.6 mmol, Fluka), and a solution of {2-[(2,6-dichlorophenyl)methyl]-1,3-thiazol-4-yl}-methan-1-ol (1.6 g, 5.9 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was heated at reflux overnight, filtered while hot through a pad of Celite[®], and the filtrate was concentrated in vacuo. Purification of the residue by silica gel chromatography (9% EtOAc in hexane) provided the title compound as a white solid. MS (ESI, pos. ion) m/z : 272 (M+1).



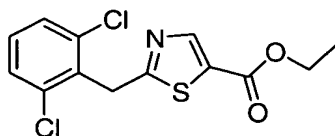
(c) 2-[(2,6-Dichlorophenyl)methyl]-4-[6-(trifluoromethyl)benzimidazol-2-yl]-1,3-thiazole. To a 25-mL, round-bottomed flask was added {2-[(2,6-dichlorophenyl)methyl]-1,3-thiazol-4-yl} formaldehyde (0.27 g, 1.0 mmol), 4-(trifluoromethyl)-1,2-phenylenediamine (0.18 g, 1.0 mmol, Lancaster), and nitrobenzene (3 mL). The reaction mixture was heated at 145 °C for 2 d. Purification of the crude mixture by silica gel chromatography (9% EtOAc in hexane) provided the title compound as a white solid. MS (ESI, pos. ion) m/z : 428 (M+1). MP: 187-189 °C.

Example 9

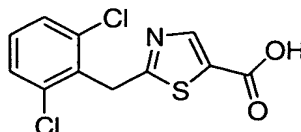
{2-[(2,6-Dichlorophenyl)methyl](1,3-thiazol-5-yl)}-N-[4-(methylethyl)phenyl]-carboxamide.



- 5 (a) Ethyl 2-chloro-3-oxopropanoate. To a 250-mL, three-necked flask equipped with a condenser and dropping funnel was added EtOH (28 mL), and sodium spheres (2.3 g, 0.1 mol). The reaction mixture was stirred at room temperature for 4 h and was diluted with ether (70 mL). A solution of ethyl formate (9.5 mL, 0.11 mol, Aldrich) and ethyl chloroacetate (12 mL, 0.11 mol, Aldrich) in ether (50 mL) was added through an addition funnel to the stirred reaction mixture. Upon completion of the addition, the mixture was stirred at room temperature overnight. The white solid was filtered, dissolved in water, acidified with 5 N HCl to pH ~4-5. The aqueous phase was extracted with ether. The organic phase was dried over Na₂SO₄, filtered and concentrated in vacuo to afford a colorless oil.

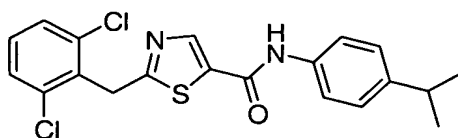


- 20 (b) Ethyl 2-[(2,6-dichlorophenyl)methyl]-1,3-thiazole-5-carboxylate. According to the procedure described in step (a) of **Example 7**, the title compound was obtained from ethyl 2-chloro-3-oxopropanoate (1.0 g, 6.7 mmol) and 2-(2,6-dichlorophenyl)ethanethioamide (1.5 g, 6.7 mmol, Maybridge) in EtOH (10 mL) as a light yellow oil. MS (ESI, pos. ion) *m/z*: 316 (M+1).



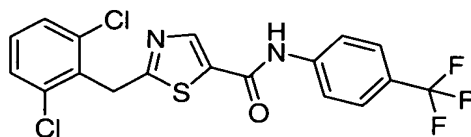
- 25 (c) 2-[(2,6-Dichlorophenyl)methyl]-1,3-thiazole-5-carboxylic acid. To a round-bottomed flask containing ethyl 2-[(2,6-dichlorophenyl)methyl]-1,3-thiazole-5-carboxylate (0.68 g, 2.16 mmol) was added THF (3 mL), H₂O (1 mL), MeOH (1

mL), and NaOH (0.43 g, 10.79 mmol). The reaction mixture was stirred at room temperature overnight, then concentrated in vacuo. The residue was dissolved in water. The aqueous phase was extracted with hexane and acidified with 5 N HCl to pH<6. The resulting white solid was filtered and the aqueous solution was
5 extracted with CHCl₃. The combined CHCl₃ extracts were dried over Na₂SO₄, filtered and concentrated to provide a white solid. The two batches of white solid were combined and dried in vacuo to provide the title compound. MS (ESI, pos. ion) *m/z*: 288 (M+1).

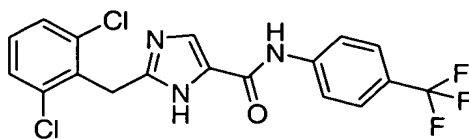


- 10 (d) {2-[(2,6-Dichlorophenyl)methyl](1,3-thiazol-5-yl)}-N-[4-(methylethyl)-phenyl]carboxamide. According to the procedure described in step (c) of **Example 7**, the title compound was obtained from 2-[(2,6-dichlorophenyl)methyl]-1,3-thiazole-5-carboxylic acid (0.15 g, 0.52 mmol), and 4-isopropylaniline (0.07 g, 0.52 mmol, Aldrich) as a white solid. MS (ESI, pos.
15 ion) *m/z*: 405 (M+1). MP: 169-175 °C.

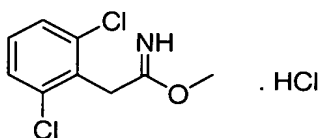
Example 10



- (e) {2-[(2,6-Dichlorophenyl)methyl](1,3-thiazol-5-yl)}-N-[4-(trifluoromethyl)-phenyl]carboxamide. According to the procedure described for **Example 9**, the
20 title compound was obtained from 2-[(2,6-dichlorophenyl)methyl]-1,3-thiazole-5-carboxylic acid, Example 9 (c), (0.15 mg, 0.52 mmol) and 4-(trifluoromethyl)aniline (84.2 mg, 0.52 mmol, Aldrich) as a white solid. MS (ESI, pos. ion) *m/z*: 431 (M+1). MP: 163-164 °C.

Example 11

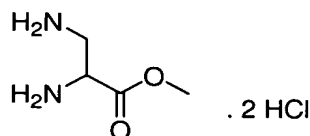
{2-[(2,6-Dichlorophenyl)methyl]imidazol-5-yl}-N-[4-(trifluoromethyl)phenyl]carboxamide.



5

(a) 2-(2,6-dichlorophenyl)-1-methoxyethanimine hydrochloride. To a 100-mL, 3-necked flask in ice-bath was added ether (50 mL), and MeOH (5 mL). After HCl gas was bubbled into the flask for 15 min, 2,6-dichlorophenylacetonitrile (3.0 g, 16.1 mmol, Aldrich) was added. The reaction solution was gradually warmed to room temperature and stirred overnight. The precipitate in the reaction mixture was filtered, washed with ether, and dried in vacuo to afford the title compound as a white solid. MS (ESI, pos. ion) m/z : 218 (M+1).

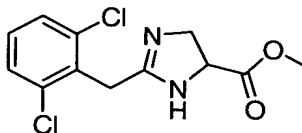
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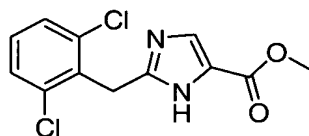
(b) Methyl 2,3-diaminopropanoate dihydrochloride. To an ice-cooled, 500-mL, round-bottomed flask equipped with a condenser was added MeOH (260 mL). After oxalyl chloride (25 mL, 286.6 mmol, Aldrich) was added slowly through a syringe, the ice bath was removed and 2,3-diaminopropanoic acid monohydrochloride (9.16 g, 65.4 mmol, Aldrich) was added. The reaction mixture was heated at 60 °C overnight, and concentrated in vacuo. The resulting solid was washed with EtOAc and CH₂Cl₂. The title compound was obtained as a white solid. MS (ESI, pos. ion) m/z : 119 (M+1).

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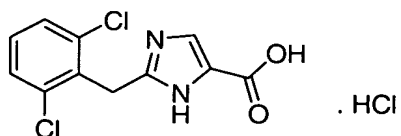


(c) Methyl 2-[(2,6-dichlorophenyl)methyl]-2-imidazoline-5-carboxylate. To a 150-mL, round-bottomed flask was added 2-(2,6-dichlorophenyl)-1-methoxy-

ethanimine hydrochloride (2.0 g, 7.87 mmol), methyl 2,3-diaminopropanoate dihydrochloride (1.5 g, 7.87 mmol), MeOH (40 mL) and triethylamine (3.3 mL, 27.56 mmol, Aldrich). The reaction mixture was stirred at room temperature overnight, and concentrated in vacuo. The residue was diluted with NaHCO₃ solution and extracted with CH₂Cl₂ (4 x). The combined organic phase was dried over Na₂SO₄, filtered and concentrated in vacuo. Purification by silica gel chromatography (4% MeOH in CH₂Cl₂) provided the title compound as a white solid. MS (ESI, pos. ion) *m/z*: 287 (M+1).

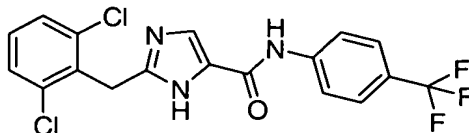


(d) Methyl 2-[(2,6-dichlorophenyl)methyl]imidazole-5-carboxylate. To a round-bottomed flask equipped with a condenser was added CH₂Cl₂ (10 mL), MnO₂ (8.5 g, 98 mmol, Fluka), and a solution of methyl 2-[(2,6-dichlorophenyl)methyl]-2-imidazoline-5-carboxylate (1.4 g, 4.9 mmol) in CH₂Cl₂ (10 mL). The mixture was heated at reflux overnight. The solid was filtered through a pad of Celite[®] and washed with MeOH and CH₂Cl₂. The combined filtrate was concentrated in vacuo. Purification by silica gel chromatography (15% EtOAc in hexane, followed by 4% MeOH in CH₂Cl₂) provided the title compound as a white solid. MS (ESI, pos. ion) *m/z*: 285 (M+1).



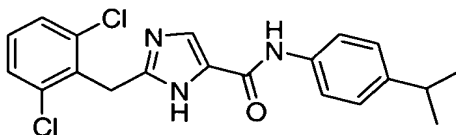
(e) 2-[(2,6-Dichlorophenyl)methyl]imidazole-5-carboxylic acid hydrochloride. To a round-bottomed flask containing methyl 2-[(2,6-dichlorophenyl)methyl]-imidazole-5-carboxylate (0.64 g, 2.25 mmol) was added THF (3 mL), MeOH (1 mL), NaOH (0.45 g, 11.27 mmol) and water (1 mL). After the reaction mixture was stirred at room temperature overnight, it was heated at reflux for 4 h, concentrated in vacuo and acidified with 5N HCl aqueous solution. The white precipitate was filtered as the first batch of product. The mother liquor was put in freezer at -20 °C overnight. The second batch of white precipitate was filtered to

provide another portion of the title compound. MS (ESI, pos. ion) m/z : 271 (M+1).



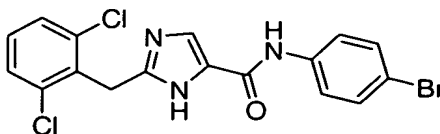
(f) {2-[(2,6-Dichlorophenyl)methyl]imidazol-5-yl}-N-[4-(trifluoromethyl)-
5 phenyl]carboxamide. To a 20-mL vial was added 2-[(2,6-dichlorophenyl)-
methyl]imidazole-5-carboxylic acid hydrochloride (100 mg, 0.32 mmol), DMF (1
mL), HATU:[o-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium] hexafluoro-
phosphate (160 mg, 0.42 mmol, Perseptive Biosystems), diisopropylethylamine
(0.17 mL, 0.97 mmol, Aldrich), and 4-(trifluoromethyl)aniline (0.10 g, 0.65
10 mmol, Aldrich). The reaction mixture was stirred at room temperature for 4 d,
diluted with EtOAc (50 mL), washed with satd NaHCO₃ (2 x), and brine, dried
over Na₂SO₄, filtered and concentrated in vacuo. Purification by silica gel
chromatography (30% EtOAc in hexane) provided the title product as white solid.
MS (ESI, pos. ion) m/z : 415 (M+1). MP: 253-255 °C.

15 Example 12



{2-[(2,6-Dichlorophenyl)methyl]imidazol-5-yl}-N-[4-(methylethyl)phenyl]-
carboxamide. According to the procedure described for **Example 11**, the title
product was obtained from 2-[(2,6-dichlorophenyl)methyl]imidazole-5-carboxylic
20 acid hydrochloride, Example 11(e), (100 mg, 0.32 mmol) and 4-isopropylaniline
(0.09 mL, 0.65 mmol, Aldrich) as a white solid. MS (ESI, pos. ion) m/z : 388, 390
(M+1). MP: 210-212 °C.

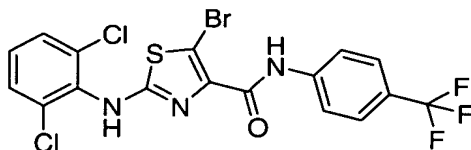
Example 13



25 {2-[(2,6-Dichlorophenyl)methyl]imidazol-5-yl}-N-(4-bromophenyl)carboxamide.
According to the procedure described for **Example 11**, the title product was

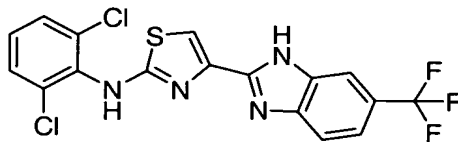
obtained from 2-[(2,6-dichlorophenyl)methyl]imidazole-5-carboxylic acid hydrochloride, Example 11(e), (100 mg, 0.32 mmol) and 4-bromoaniline (111 mg, 0.65 mmol, Aldrich) as a white solid. MS (ESI, pos. ion) m/z : 426 (M+1). MP: 253-254 °C.

5 Example 14

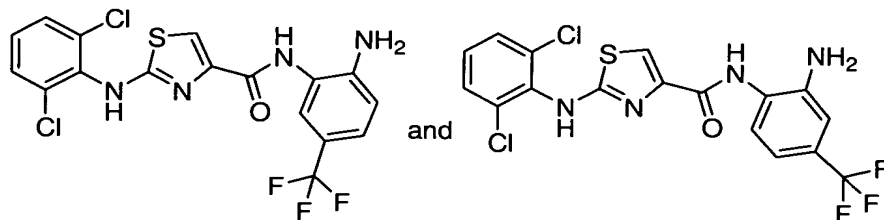


{2-[(2,6-Dichlorophenyl)amino]-5-bromo(1,3-thiazol-4-yl)}-N-[4-(trifluoromethyl)phenyl]carboxamide. To a 50-mL flask was added {2-[(2,6-dichlorophenyl)amino](1,3-thiazol-4-yl)}-N-[4-(trifluoromethyl)phenyl]-carboxamide, Example 63, (100 mg, 0.23 mmol), acetic acid (2.0 mL), and bromine (0.03 mL, 0.46 mmol, Aldrich). The reaction mixture was stirred at room temperature overnight, then concentrated in vacuo. The crude product was diluted with CH₂Cl₂ (50 mL), washed with satd NaHCO₃ (2 x), 1 M Na₂S₂O₃ and brine, dried over Na₂SO₄, filtered and concentrated in vacuo. Purification by silica gel chromatography (12% EtOAc in hexane) provided the title product as an off-white solid. MS (ESI, pos. ion) m/z : 512 (M+1). MP: 151-162 °C.

Example 15

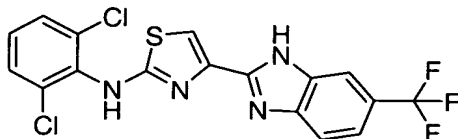


(2,6-Dichloro-phenyl)-[4-(6-trifluoromethyl-1H-benzoimidazol-2-yl)-thiazol-2-yl]-amine.



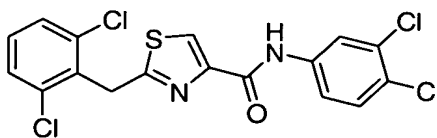
(a) N-[2-Amino-5-(trifluoromethyl)phenyl]{2-[(2,6-dichlorophenyl)amino](1,3-thiazol-4-yl)}carboxamide and N-[2-amino-4-(trifluoromethyl)phenyl]{2-[(2,6-dichlorophenyl)amino](1,3-thiazol-4-yl)}carboxamide. According to the

procedure described in step (f) of **Example 11**, the title compounds were obtained from 2-[(2,6-dichlorophenyl)amino]-1,3-thiazole-4-carboxylic acid (339 mg, 1.18 mmol, prepared analogously to the procedures described in Example 3) and 4-(trifluoromethyl)-1,2-phenylenediamine (207 mg, 1.18 mmol, Lancaster) as a light brown solid. MS (ESI, pos. ion) m/z : 447 (M+1).

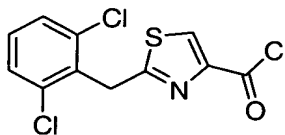


(b) (2,6-Dichloro-phenyl)-[4-(6-trifluoromethyl-1H-benzimidazol-2-yl)-thiazol-2-yl]-amine. A solution of N-[2-amino-5-(trifluoromethyl)phenyl]{2-[(2,6-dichlorophenyl)amino](1,3-thiazol-4-yl)}carboxamide and N-[2-amino-4-(trifluoromethyl)phenyl]{2-[(2,6-dichlorophenyl)amino](1,3-thiazol-4-yl)}carboxamide (0.19 g, 0.43 mmol) in acetic acid (4 mL), and toluene (1 mL) was heated at 100 °C for 1 h, then concentrated in vacuo. The acetic acid was neutralized with satd NaHCO₃. The aqueous phase was extracted with EtOAc. The combined organic phase was dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was diluted with CH₂Cl₂, and the resulting white precipitate was filtered and dried in vacuo to provide the title compound. MS (ESI, pos. ion) m/z : 429 (M+1). MP: 242-243 °C.

Example 16

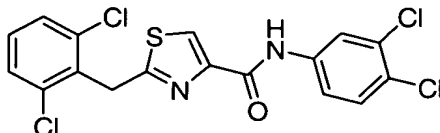


N-(3,4-Dichlorophenyl){2-[(2,6-dichlorophenyl)methyl](1,3-thiazol-4-yl)}carboxamide.



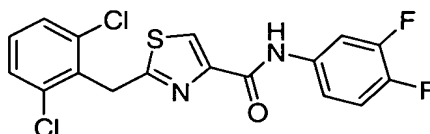
(a) 2-[(2,6-Dichlorophenyl)methyl]-1,3-thiazole-4-carbonyl chloride. To a round-bottomed flask with 2-[(2,6-dichlorophenyl)methyl]-1,3-thiazole-4-carboxylic acid, Example 9 (c), (1.0 g, 3.48 mmol) was added CH₂Cl₂, oxalyl chloride (2.0 M solution in CH₂Cl₂, 2.1 mL, 4.2 mmol, Aldrich), and three drops of DMF. The

mixture was heated at reflux overnight, concentrated in vacuo to provide the crude product as a light-yellow solid.



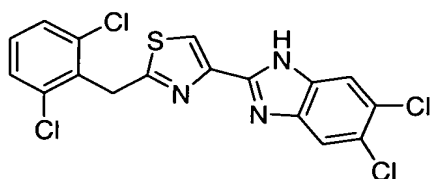
- (b) N-(3,4-Dichlorophenyl){2-[(2,6-dichlorophenyl)methyl](1,3-thiazol-4-yl)}carboxamide. According to the procedure described for **Example 1**, the title product was obtained from 2-[(2,6-dichlorophenyl)methyl]-1,3-thiazole-4-carbonyl chloride (0.15 g, 0.49 mmol) and 3,4-dichloroaniline (0.08 g, 0.49 mmol, Avocado) as a white solid. MS (ESI, pos. ion) m/z : 430 (M-1). MP: 153-157 °C.

Example 17

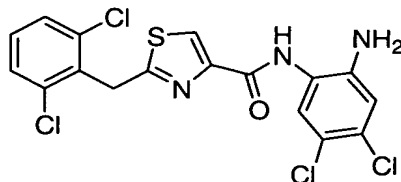


- {2-[(2,6-Dichlorophenyl)methyl](1,3-thiazol-4-yl)}-N-(3,4-difluorophenyl)-carboxamide. According to the procedure described for **Example 16**, the title product was obtained from 2-[(2,6-dichlorophenyl)methyl]-1,3-thiazole-4-carbonyl chloride (0.15 g, 0.49 mmol) and 3,4-difluoroaniline (63 mg, 0.49 mmol, Aldrich) as a white solid. MS (ESI, pos. ion) m/z : 399 (M-1). MP: 113-116 °C.

Example 18

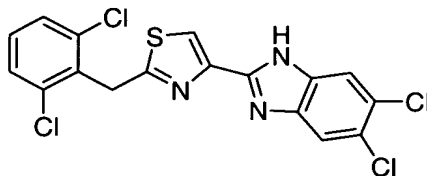


4-(5,6-Dichlorobenzimidazol-2-yl)-2-[(2,6-dichlorophenyl)methyl]-1,3-thiazole.



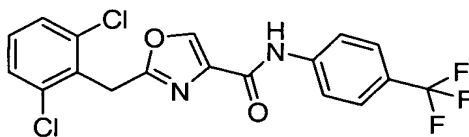
- (a) N-(2-Amino-4,5-dichlorophenyl){2-[(2,6-dichlorophenyl)methyl](1,3-thiazol-4-yl)}carboxamide. According to the procedure described in step (b) of **Example 16**, the title product was obtained from 2-[(2,6-dichlorophenyl)methyl]-1,3-thiazole-4-carbonyl chloride (155.6 mg, 0.51 mmol) and 4,5-dichloro-

1,2-phenylenediamine (0.174 g, 0.98 mmol, Aldrich) as a brown solid. MS (ESI, pos. ion) m/z : 448 (M+1). MP: 238-241 °C.

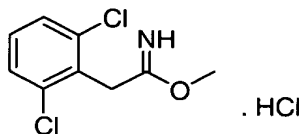


(b) 4-(5,6-Dichlorobenzimidazol-2-yl)-2-[(2,6-dichlorophenyl)methyl]-1,3-thiazole. To a round-bottomed flask containing N-(2-amino-4,5-dichlorophenyl){2-[(2,6-dichlorophenyl)methyl](1,3-thiazol-4-yl)}carboxamide (200 mg, 0.45 mmol) was added acetic acid (4 mL), and toluene (1 mL). The solution was heated to 100 °C for 1 h, and concentrated in vacuo. The acetic acid was neutralized with satd NaHCO₃. The aqueous phase was extracted with EtOAc. The combined organic phase was dried over Na₂SO₄, filtered and concentrated in vacuo. Purification by silica gel chromatography (14% EtOAc in hexane), followed by Prep HPLC (50%-95% CH₃CN/H₂O), provided the title product as a white solid. MS (ESI, pos. ion) m/z : 430 (M+1). MP: 245-247 °C.

Example 19

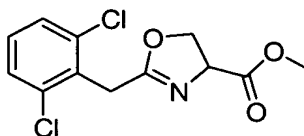


{2-[(2,6-Dichlorophenyl)methyl](1,3-oxazol-4-yl)}-N-[4-(trifluoromethyl)phenyl]carboxamide.

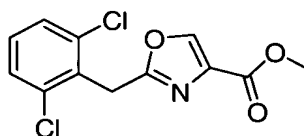


(a) 2-(2,6-Dichlorophenyl)-1-methoxyethanimine hydrochloride. To a 500-mL, three-necked, round-bottomed flask in ice bath was added 2,6-dichlorophenylacetonitrile (10.5 g, 56.4 mmol, Aldrich) and MeOH (200 mL). HCl gas was bubbled into the mixture for 90 min with inside temperature lower than 25 °C. The reaction solution was gradually warmed to room temperature and stirred for 4 h until 2,6-dichlorophenylacetonitrile was consumed. The reaction mixture was concentrated in vacuo. CH₂Cl₂ was added to the residue and was

evaporated. The addition and evaporation of CH_2Cl_2 was repeated one more time. The title compound was obtained as a white solid and was used in the next step without purification. MS (ESI, pos. ion) m/z : 218 (M+1).



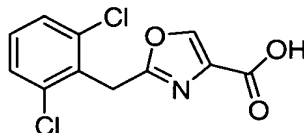
- 5 (b) Methyl 2-[(2,6-dichlorophenyl)methyl]-1,3-oxazoline-4-carboxylate. To a 250-mL, round-bottomed flask was added 2-(2,6-dichlorophenyl)-1-methoxyethanimine hydrochloride from step (a), D,L-serine methyl ester hydrochloride (8.8 g, 56.4 mmol, Aldrich), CH_2Cl_2 (115 mL), and diisopropylethylamine (10.0 mL, 56.4 mmol, Aldrich). The reaction solution was stirred at room temperature overnight, and concentrated in vacuo. The residue was diluted with CH_2Cl_2 (150 mL). The CH_2Cl_2 solution was washed with water (2 x), and brine. The organic phase was dried over Na_2SO_4 , filtered and concentrated in vacuo. Purification by silica gel chromatography (8%-19% EtOAc in hexane) provided the title product as a white solid. MS (ESI, pos. ion) m/z : 288 (M+1).



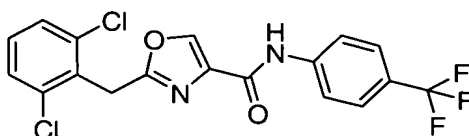
- (c) Methyl 2-[(2,6-dichlorophenyl)methyl]-1,3-oxazole-4-carboxylate. To a 250-mL, round-bottomed flask was added CH_2Cl_2 (150 mL), copper (II) bromide (3.2 g, 14.5 mmol, Aldrich), 1,8-diazabicyclo[5,4,0]undec-7-ene (2.2 g, 14.5 mmol, Aldrich), and hexamethylenetetramine (2.0 g, 14.5 mmol, Aldrich). The dark warm solution stood at room temperature for 5 min, then methyl 2-[(2,6-dichlorophenyl)methyl]-1,3-oxazoline-4-carboxylate (4.1 g, 14.5 mmol) was added. The solution was stirred at room temperature overnight, then diluted with 1:1 mixture of satd NH_4Cl and NH_4OH (total 150 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 150 mL). The combined organic phase was successively washed with 1:1 mixture of satd NH_4Cl and NH_4OH , 10% citric acid, saturated NaHCO_3 , and brine. The resulting solution was dried over Na_2SO_4 , filtered and concentrated in vacuo. Purification by silica gel chromatography

(14%-18% EtOAc in hexane) provided the title product as a light-yellow solid.

MS (ESI, pos. ion) m/z : 286, 288 (M+1).

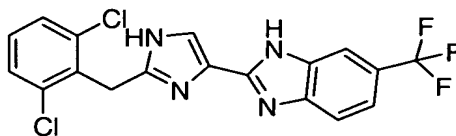


(d) 2-[(2,6-Dichlorophenyl)methyl]-1,3-oxazole-4-carboxylic acid. To a round-bottomed flask containing methyl 2-[(2,6-dichlorophenyl)methyl]-1,3-oxazole-4-carboxylate (1.93 g, 6.77 mmol) was added MeOH (15 mL), NaOH (1.35 g, 33.85 mmol) and H₂O (15 mL). The reaction mixture was stirred at room temperature for 5 h, concentrated and neutralized with 5 N HCl. The resulting white solid was filtered and dried to provide the title product. MS (ESI, pos. ion) m/z : 272, 274 (M+1).

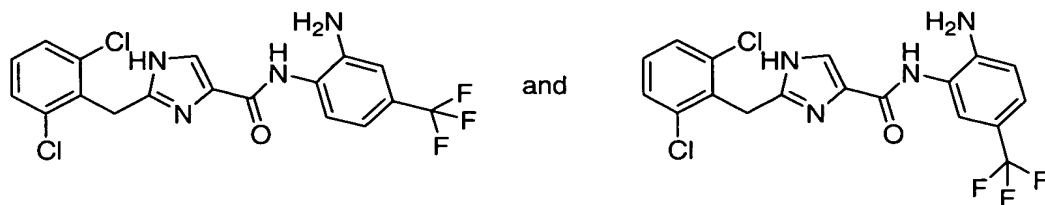


(e) {2-[(2,6-Dichlorophenyl)methyl](1,3-oxazol-4-yl)}-N-[4-(trifluoromethyl)phenyl]carboxamide. To a 100-mL, round-bottomed flask was added 2-[(2,6-dichlorophenyl)methyl]-1,3-oxazole-4-carboxylic acid (0.22 g, 0.81 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.23 g, 1.22 mmol, Aldrich), 1-hydroxybenzotriazole (0.11 g, 0.81 mmol, Aldrich), CH₂Cl₂ (4 mL) and 4-(trifluoromethyl)aniline (0.15 mL, 1.22 mmol, Aldrich). The reaction mixture was stirred at room temperature overnight and diluted with CH₂Cl₂ (50 mL). The organic phase was washed with NaHCO₃ (2 x), H₂O and brine, dried over Na₂SO₄, filtered and concentrated in vacuo. Purification by silica gel chromatography (5%-8% EtOAc in hexane) provided the title product as a white solid. MS (ESI, pos. ion) m/z : 413, 415 (M+1). MP: 182-184 °C.

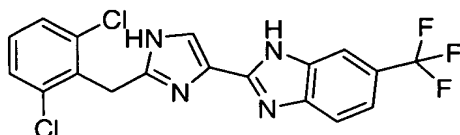
Example 20



2-{2-[(2,6-Dichlorophenyl)methyl]imidazol-4-yl}-6-(trifluoromethyl)benzimidazole.



(a) N-[2-Amino-4-(trifluoromethyl)phenyl]{2-[(2,6-dichlorophenyl)-methyl]imidazol-4-yl}carboxamide and N-[2-amino-5-(trifluoromethyl)-phenyl]{2-[(2,6-dichlorophenyl)methyl]imidazol-4-yl}carboxamide. According to the procedure described in step (e) of **Example 19**, the title products were obtained from 4-(trifluoromethyl)-1,2-phenylenediamine (0.17 g, 0.97 mmol, Lancaster) and 2-[(2,6-dichlorophenyl)methyl]imidazole-5-carboxylic acid hydrochloride (0.263 g, 0.97 mmol, Example 11 (e)) as an off-white solid. MS (ESI, pos. ion) m/z : 429 (M+1).

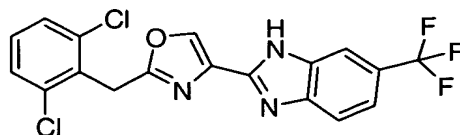


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(b) 2-{2-[(2,6-Dichlorophenyl)methyl]imidazol-4-yl}-6-(trifluoromethyl)-benzimidazole. According to the procedure described in step (b) of **Example 15**, the title product was obtained from N-[2-amino-4-(trifluoromethyl)-phenyl]{2-[(2,6-dichlorophenyl)methyl]imidazol-4-yl}carboxamide and N-[2-amino-5-(trifluoromethyl)phenyl]{2-[(2,6-dichlorophenyl)methyl]imidazol-4-yl}carboxamide (0.14 mg, 0.33 mmol) as a white solid. MS (ESI, pos. ion) m/z : 411, 413 (M+1). MP: 281-282 °C.

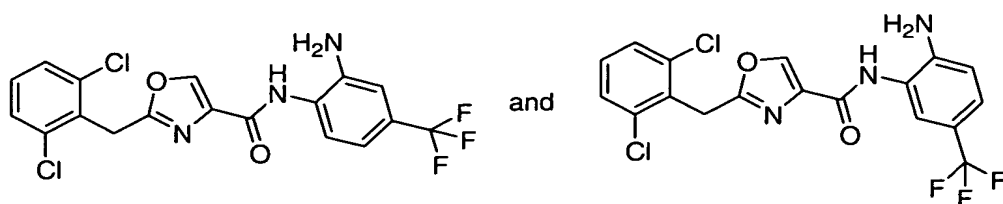
15

Example 21

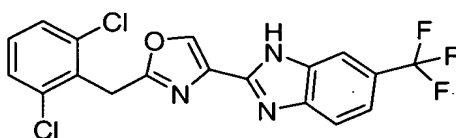


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2-[(2,6-Dichlorophenyl)methyl]-4-[6-(trifluoromethyl)benzimidazol-2-yl]-1,3-oxazole.



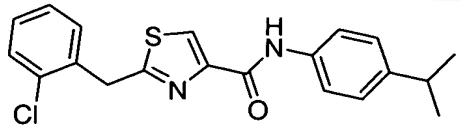
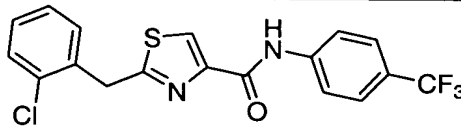
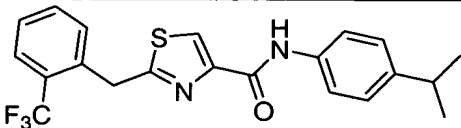
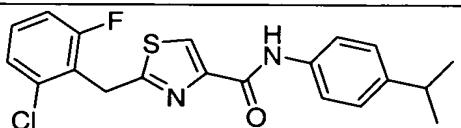
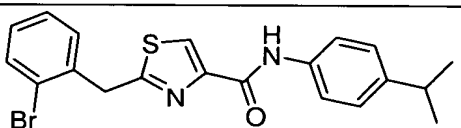
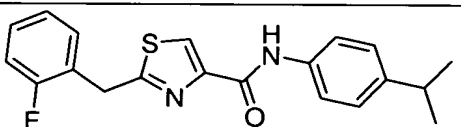
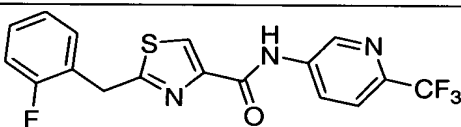
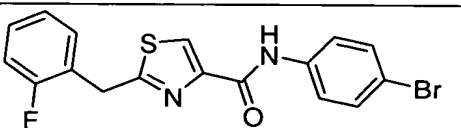
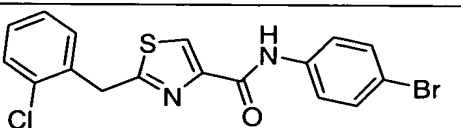
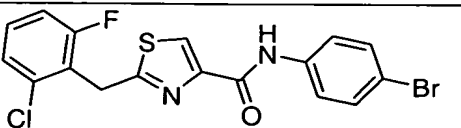
- (a) N-[2-Amino-4-(trifluoromethyl)phenyl]{2-[(2,6-dichlorophenyl)methyl](1,3-oxazol-4-yl)}carboxamide and N-[2-amino-5-(trifluoromethyl)phenyl]{2-[(2,6-dichlorophenyl)methyl](1,3-oxazol-4-yl)}carboxamide. According to the procedure described in step (e) of **Example 19**, the title product was obtained from 2-[(2,6-dichlorophenyl)methyl]-1,3-oxazole-4-carboxylic acid, Example 19 (d), (0.26 g, 0.97 mmol) and 4-(trifluoromethyl)-1,2-phenylenediamine (0.17 g, 0.97 mmol, Lancaster) as a light-brown solid. MS (ESI, pos. ion) m/z : 430 (M+1).

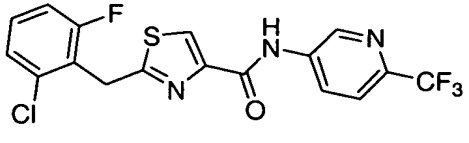
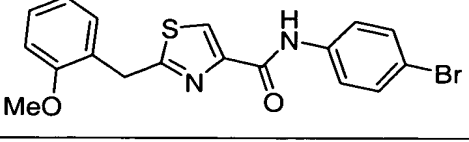
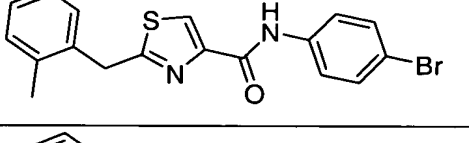
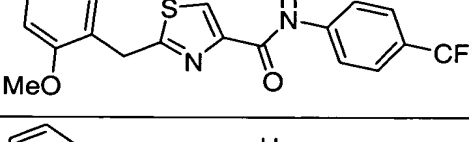
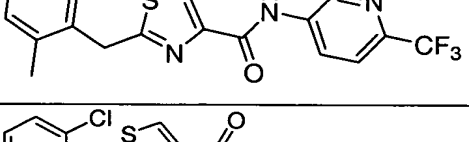
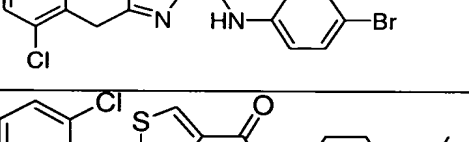
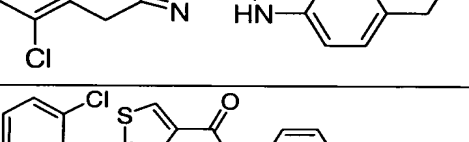
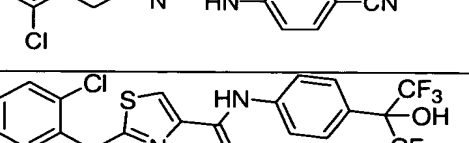
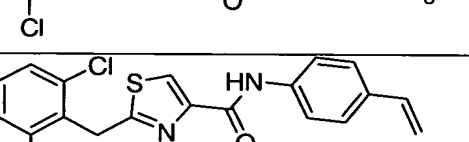
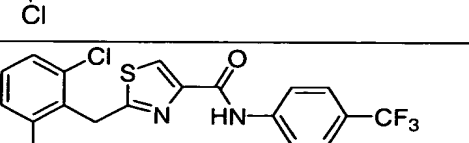



- (b) 2-[(2,6-Dichlorophenyl)methyl]-4-[6-(trifluoromethyl)benzimidazol-2-yl]-1,3-oxazole. According to the procedure described in step (b) of **Example 15**, the title product was obtained from N-[2-amino-4-(trifluoromethyl)phenyl]{2-[(2,6-dichlorophenyl)methyl](1,3-oxazol-4-yl)}carboxamide and N-[2-amino-5-(trifluoromethyl)phenyl]{2-[(2,6-dichlorophenyl)methyl](1,3-oxazol-4-yl)}carboxamide (0.19 mg, 44 mmol) as a white solid. MS (ESI, pos. ion) m/z : 412, 414 (M+1). MP: 201-202 °C.

Table 1: The following compounds were prepared by the methods outlined in Scheme 1 and analogous to the experimental procedure described in Example 1.

Ex.	Structure	MW	MS (ESI)	MP (°C)	Method
22		405.3	406	98.8-106.9	1
23		394.3	395	137.7-138.8	1
24		432.3	433	139.1-147.1	1

25		370.9	372	85.4-92.7	1
26		396.8	398	85.5-94.0	1
27		404.5	405	NA	1
28		388.9	309	NA	1
29		415.4	416	NA	1
30		354.4	355	NA	1
31		381.4	382	104.8-107.7	1
32		391.3	392	100.8-101	1
33		407.7	409	109.4-110.6	1
34		425.7	427	111.8-112.5	1

35		415.8	417	123.4-125.1	1
36		403.3	404	138.0-138.4	1
37		387.3	388	121.9-123.4	1
38		392.4	393	107.2-108.2	1
39		377.4	378	140.2-141.3	1
40		439.9	442.7	126.6-132.0	1
41		390.0	390.9		1
42		387.0	387.8		1
43		527.9	528.9	197.0-197.8	1
44		388.0	388.9		1
45		429.9	431.0		1

46		418.0	419.1		1
47		479.9	481.1	95.0-96.4	1
48		386.0	386.7	150.0-239.5	1
49		419.3	419 (M+1)	139-141	1
50		406.3	406 (M+1)	172-174	1

Table 2: The following compounds were prepared by the methods outlined in Scheme 2 and analogous to the experimental procedures described in Examples 2 and 3.

Ex.	Structure	MW	MS (ESI)	MP (°C)	Method
51		398.8	400	232.5-234.3	2
52		409.7	411	214.7-216.2	2
53		444.1	445	194.9-196.6	2
54		479.05	480.1	158.0-160.0	2

55		390.98	391.8	198.4-199.7	2
56		443.15	443.7	125.9-126.9	2
57		405.05	405.9	85.5-152.5	2
58		355.43	355.9	136.5-180.1	2
59		431.98	432.9	175.7-247.0	2
60		406.95	409.7	220.5-221.3	2
61		397.03	397.9	192.5-193.1	2
62		479.05	480.1	158.0-160.0	2
63		432.3	430 (M-1)	199-200	2
64		365	366 (M+1)	128-133	2
65		402.3	402 (M+1)	208-209	2

66		431.36	432 (M+1)	128-130	2
67		405.44	406 (M+1)	96-100	2
68		442.26	442 (M+1)	151-153	2
69		476.7	476 (M+1)	262-264	2
70		439.89	440 (M+1)	216-218	2
71		465.8	464 (M-1)	243-244	2

Table 3: The following compounds were prepared by the methods outlined in Scheme 3 and analogous to the experimental procedures described in Example 4.

Ex.	Structure	MW	MS (ESI)	MP (°C)	Method
72		428.36	429 (M+1)	211-212	3
73		462.8	463 (M+1)	188-210	3

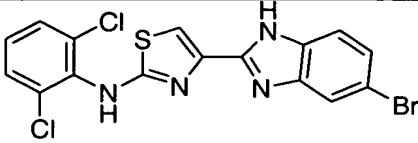
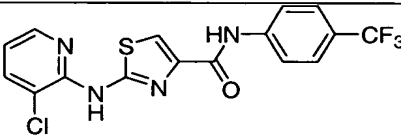
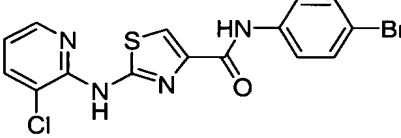
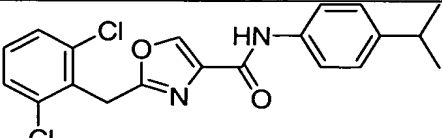
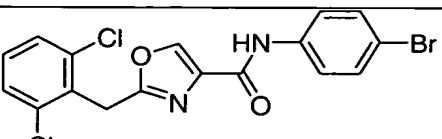
74		440.15	441 (M+1)	267-268	3
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Table 4: The following compounds were prepared by the methods outlined in Scheme 11 and analogous to the experimental procedure described in Example 5.

Ex	Structure	MW	MS (ESI)	MP (°C)	Method
75		398.8	399 (M+1)	186-187	11
76		409.09	409 (M+1)	226-258	11

- 5 Table 5: The following compounds were prepared by the methods outlined in Scheme 14 and analogous to the experimental procedure described in Example 19.

Ex.	Structure	MW	MS (ESI)	MP (°C)	Method
77		389.28	394 (M+1)	137-139	14
78		426.10	427 (M+1)	164-165	14

Capsaicin-induced Ca²⁺ influx in primary dorsal root ganglion neurons

- 10 Embryonic 19 day old (E19) dorsal root ganglia (DRG) were dissected from timed-pregnant, terminally anesthetized Sprague-Dawley rats (Charles River, Wilmington, MA) and collected in ice-cold L-15 media (Life Technologies,

Grand Island, NY) containing 5% heat inactivated horse serum (Life Technologies). The DRG were then dissociated into single cell suspension using a papain dissociation system (Worthington Biochemical Corp., Freehold, NJ). The dissociated cells were pelleted at 200 x g for 5 min and re-suspended in EBSS containing 1 mg/mL ovomucoid inhibitor, 1 mg/mL ovalbumin and 0.005% DNase. Cell suspension was centrifuged through a gradient solution containing 10 mg/mL ovomucoid inhibitor, 10 mg/mL ovalbumin at 200 x g for 6 min to remove cell debris; and filtered through a 88- μ m nylon mesh (Fisher Scientific, Pittsburgh, PA) to remove any clumps. Cell number was determined with a hemocytometer and cells were seeded into poly-ornithine 100 μ g/mL (Sigma) and mouse laminin 1 μ g/mL (Life Technologies)-coated 96-well plates at 10×10^3 cells/well in complete medium. The complete medium consists of minimal essential medium (MEM) and Ham's F12, 1:1, penicillin (100 U/mL), and streptomycin (100 μ g/mL), and nerve growth factor (10ng/mL), 10% heat inactivated horse serum (Life Technologies). The cultures were kept at 37 °C, 5% CO₂ and 100% humidity. For controlling the growth of non-neuronal cells, 5-fluoro-2'-deoxyuridine (75 μ M) and uridine (180 μ M) were included in the medium. Activation of VR1 was achieved in these cellular assays using either a capsaicin stimulus (ranging from 0.01-10 μ M) or by an acid stimulus (addition of 30mM Hepes/Mes buffered at pH 4.1). Compounds were also tested in an assay format to evaluate their agonist properties at VR1. The activation of VR1 is followed as a function of cellular uptake of radioactive calcium (⁴⁵Ca²⁺; Amersham CES3-2mCi).

Capsaicin Antagonist Assay: E-19 DRG cells at 3 days in culture are incubated with serial concentrations of VR1 antagonists, in HBSS (Hanks buffered saline solution supplemented with BSA 0.1 mg/mL and 1 mM Hepes at pH 7.4) for 15 min, room temperature. Cells are then challenged with a VR1 agonist, capsaicin (500 nM), in activation buffer containing 0.1mg/mL BSA, 15 mM Hepes, pH 7.4, and 10 μ Ci/mL ⁴⁵Ca²⁺ (Amersham CES3-2mCi) in Ham's F12 for 2 min at room temperature.

Acid Antagonist Assay: Compounds are pre-incubated with E-19 DRG cells at room temperature for 2 minutes prior to addition of ⁴⁵Ca²⁺ in 30mM Hepes/Mes

buffer (Final Assay pH 5) and then left for an additional 2 minutes prior to compound washout. Final concentration of $^{45}\text{Ca}^{2+}$ (Amersham CES3-2mCi) is 10 $\mu\text{Ci/mL}$.

Agonist Assay: Compounds are incubated with E-19 DRG cells at room temperature for 2 minutes in the presence of $^{45}\text{Ca}^{2+}$ prior to compound washout. Final $^{45}\text{Ca}^{2+}$ (Amersham CES3-2mCi) at 10 $\mu\text{Ci/mL}$.

Compound Washout and Analysis: Assay plates are washed using an ELX405 plate washer (Bio-Tek Instruments Inc.) immediately after functional assay. Wash 3 X with PBS, 0.1 mg/mL BSA. Aspirate between washes. Read plates using a MicroBeta Jet (Wallac Inc.). Compound activity is then calculated using appropriate computational algorithms.

$^{45}\text{Calcium}^{2+}$ Assay Protocol

Compounds may be assayed using Chinese Hamster Ovary cell lines stably expressing either human VR1 or rat VR1 under a CMV promoter. Cells could be cultured in a Growth Medium, routinely passaged at 70% confluency using trypsin and plated in an assay plate 24 hours prior to compound evaluation.

Possible Growth Medium:

DMEM, high glucose (Gibco 11965-084).
10% Dialyzed serum (Hyclone SH30079.03).
1X Non-Essential Amino Acids (Gibco 11140-050).
1X Glutamine-Pen-Strep (Gibco 10378-016).
Geneticin, 450 $\mu\text{g/mL}$ (Gibco 10131-035).

Compounds could be diluted in 100% DMSO and tested for activity over several log units of concentration [40 μM -2pM]. Compounds may be further diluted in HBSS buffer (pH 7.4) 0.1 mg/mL BSA, prior to evaluation. Final DMSO concentration in assay would be 0.5-1%. Each assay plate could be controlled with a buffer only and a known antagonist compound (either capsazepine or one of the described VR1 antagonists).

Activation of VR1 could be achieved in these cellular assays using either a capsaicin stimulus (ranging from 0.1-1 μM) or by an acid stimulus (addition of 30mM Hepes/Mes buffered at pH 4.1). Compounds could also be tested in an assay format to evaluate their agonist properties at VR1.

Capsaicin Antagonist Assay: Compounds may be pre-incubated with cells (expressing either human or rat VR1) at room temperature for 2 minutes prior to addition of $^{45}\text{Ca}^{2+}$ and Capsaicin and then left for an additional 2 minutes prior to compound washout. Capsaicin (200nM) can be added in HAM's F12, 0.1 mg/mL BSA, 15 mM Hepes at pH 7.4. Final $^{45}\text{Ca}^{2+}$ (Amersham CES3-2mCi) added could be $10\mu\text{Ci/mL}$.

Acid Antagonist Assay: Compounds can be pre-incubated with cells (expressing either human or rat VR1) for 2 minutes prior to addition of $^{45}\text{Ca}^{2+}$ in 30mM Hepes/Mes buffer (Final Assay pH 5) and then left for an additional 2 minutes prior to compound washout. Final $^{45}\text{Ca}^{2+}$ (Amersham CES3-2mCi) added could be $10\mu\text{Ci/mL}$.

Agonist Assay: Compounds can be incubated with cells (expressing either human or rat VR1) for 2 minutes in the presence of $^{45}\text{Ca}^{2+}$ prior to compound washout. Final $^{45}\text{Ca}^{2+}$ (Amersham CES3-2mCi) added could be $10\mu\text{Ci/mL}$.

Compound Washout and Analysis: Assay plates would be washed using an ELX405 plate washer (Bio-Tek Instruments Inc.) immediately after the functional assay. One could wash 3 X with PBS, 0.1 mg/mL BSA, aspirating between washes. Plates could then be read using a MicroBeta Jet (Wallac Inc.) and compound activity calculated using appropriate computational algorithms.

Useful nucleic acid sequences and proteins may be found in U.S. Patent Nos. 6,335,180, 6, 406,908 and 6,239,267, herein incorporated by reference in their entirety.

For the treatment of vanilloid-receptor-diseases, such as acute, inflammatory and neuropathic pain, dental pain, general headache, migraine, cluster headache, mixed-vascular and non-vascular syndromes, tension headache, general inflammation, arthritis, rheumatic diseases, osteoarthritis, inflammatory bowel disorders, inflammatory eye disorders, inflammatory or unstable bladder disorders, psoriasis, skin complaints with inflammatory components, chronic inflammatory conditions, inflammatory pain and associated hyperalgesia and allodynia, neuropathic pain and associated hyperalgesia and allodynia, diabetic neuropathy pain, causalgia, sympathetically maintained pain, deafferentation syndromes, asthma, epithelial tissue damage or dysfunction, herpes simplex,

disturbances of visceral motility at respiratory, genitourinary, gastrointestinal or vascular regions, wounds, burns, allergic skin reactions, pruritus, vitiligo, general gastrointestinal disorders, gastric ulceration, duodenal ulcers, diarrhea, gastric lesions induced by necrotising agents, hair growth, vasomotor or allergic rhinitis, 5 bronchial disorders or bladder disorders, the compounds of the present invention may be administered orally, parentally, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional pharmaceutically acceptable carriers, adjuvants, and vehicles. The term parenteral as used herein includes, subcutaneous, intravenous, intramuscular, intrasternal, infusion techniques or 10 intraperitoneally.

Treatment of diseases and disorders herein is intended to also include the prophylactic administration of a compound of the invention, a pharmaceutical salt thereof, or a pharmaceutical composition of either to a subject (*i.e.*, an animal, preferably a mammal, most preferably a human) believed to be in need of 15 preventative treatment, such as, for example, pain, inflammation and the like.

The present compounds may also be used in combination therapies with opioids and other anti-pain analgesics, including narcotic analgesics, Mu receptor antagonists, Kappa receptor antagonists, non-narcotic (*i.e.* non-addictive) analgesics, monoamine uptake inhibitors, adenosine regulating agents, 20 cannabinoid derivatives, Substance P antagonists, neurokinin-1 receptor antagonists, COX-2 inhibitors such as celecoxib, rofecoxib, valdecoxib, parecoxib, and darecoxib, NSAID's, and sodium channel blockers, among others. More preferred would be combinations with compounds selected from morphine, meperidine, codeine, pentazocine, buprenorphine, butorphanol, dezocine, 25 meptazinol, hydrocodone, oxycodone, methadone, Tramadol [(+) enantiomer], DuP 747, Dynorphine A, Enadoline, RP-60180, HN-11608, E-2078, ICI- 204448, acetaminophen (paracetamol), propoxyphene, nalbuphine, E-4018, filenadol, mirtentanil, amitriptyline, DuP631, Tramadol [(-) enantiomer], GP-531, acadesine, AKI-1, AKI-2, GP-1683, GP-3269, 4030W92, tramadol racemate, 30 Dynorphine A, E-2078, AXC3742, SNX-111, ADL2-1294, ICI-204448, CT-3, CP-99,994, and CP-99,994.

The dosage regimen for treating vanilloid-receptor-mediated diseases, cancer, and/or hyperglycemia with the compounds of this invention and/or compositions of this invention is based on a variety of factors, including the type of disease, the age, weight, sex, medical condition of the patient, the severity of the condition, the route of administration, and the particular compound employed. Thus, the dosage regimen may vary widely, but can be determined routinely using standard methods. Dosage levels of the order from about 0.01 mg to 30 mg per kilogram of body weight per day, preferably from about 0.1 mg to 10 mg/kg, more preferably from about 0.25 mg to 1 mg/kg are useful for all methods of use disclosed herein.

The pharmaceutically active compounds of this invention can be processed in accordance with conventional methods of pharmacy to produce medicinal agents for administration to patients, including humans and other mammals.

For oral administration, the pharmaceutical composition may be in the form of, for example, a capsule, a tablet, a suspension, or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a given amount of the active ingredient. For example, these may contain an amount of active ingredient from about 1 to 2000 mg, preferably from about 1 to 500 mg, more preferably from about 5 to 150 mg. A suitable daily dose for a human or other mammal may vary widely depending on the condition of the patient and other factors, but, once again, can be determined using routine methods.

The active ingredient may also be administered by injection as a composition with suitable carriers including saline, dextrose, or water. The daily parenteral dosage regimen will be from about 0.1 to about 30 mg/kg of total body weight, preferably from about 0.1 to about 10 mg/kg, and more preferably from about 0.25 mg to 1 mg/kg.

Injectable preparations, such as sterile injectable aqueous or oleaginous suspensions, may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic

parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending
5 medium. For this purpose any bland fixed oil may be employed, including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable non-irritating excipient such as cocoa butter and
10 polyethylene glycols that are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

A suitable topical dose of active ingredient of a compound of the invention is 0.1 mg to 150 mg administered one to four, preferably one or two times daily. For topical administration, the active ingredient may comprise from
15 0.001% to 10% w/w, *e.g.*, from 1% to 2% by weight of the formulation, although it may comprise as much as 10% w/w, but preferably not more than 5% w/w, and more preferably from 0.1% to 1% of the formulation.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin (*e.g.*, liniments,
20 lotions, ointments, creams, or pastes) and drops suitable for administration to the eye, ear, or nose.

For administration, the compounds of this invention are ordinarily combined with one or more adjuvants appropriate for the indicated route of administration. The compounds may be admixed with lactose, sucrose, starch
25 powder, cellulose esters of alkanolic acids, stearic acid, talc, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, acacia, gelatin, sodium alginate, polyvinyl-pyrrolidone, and/or polyvinyl alcohol, and tableted or encapsulated for conventional administration. Alternatively, the compounds of this invention may be dissolved in saline, water, polyethylene
30 glycol, propylene glycol, ethanol, corn oil, peanut oil, cottonseed oil, sesame oil, tragacanth gum, and/or various buffers. Other adjuvants and modes of administration are well known in the pharmaceutical art. The carrier or diluent

may include time delay material, such as glyceryl monostearate or glyceryl distearate alone or with a wax, or other materials well known in the art.

The pharmaceutical compositions may be made up in a solid form (including granules, powders or suppositories) or in a liquid form (*e.g.*, solutions, suspensions, or emulsions). The pharmaceutical compositions may be subjected to conventional pharmaceutical operations such as sterilization and/or may contain conventional adjuvants, such as preservatives, stabilizers, wetting agents, emulsifiers, buffers etc.

Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose, lactose, or starch. Such dosage forms may also comprise, as in normal practice, additional substances other than inert diluents, *e.g.*, lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting, sweetening, flavoring, and perfuming agents.

Compounds of the present invention can possess one or more asymmetric carbon atoms and are thus capable of existing in the form of optical isomers as well as in the form of racemic or non-racemic mixtures thereof. The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, *e.g.*, by formation of diastereoisomeric salts, by treatment with an optically active acid or base. Examples of appropriate acids are tartaric, diacetyltartaric, dibenzoyltartaric, ditoluoyltartaric, and camphorsulfonic acid and then separation of the mixture of diastereoisomers by crystallization followed by liberation of the optically active bases from these salts. A different process for separation of optical isomers involves the use of a chiral chromatography column optimally chosen to maximize the separation of the enantiomers. Still another

available method involves synthesis of covalent diastereoisomeric molecules by reacting compounds of the invention with an optically pure acid in an activated form or an optically pure isocyanate. The synthesized diastereoisomers can be separated by conventional means such as chromatography, distillation,
5 crystallization or sublimation, and then hydrolyzed to deliver the enantiomerically pure compound. The optically active compounds of the invention can likewise be obtained by using active starting materials. These isomers may be in the form of a free acid, a free base, an ester or a salt.

Likewise, the compounds of this invention may exist as isomers, that is
10 compounds of the same molecular formula but in which the atoms, relative to one another, are arranged differently. In particular, the alkylene substituents of the compounds of this invention, are normally and preferably arranged and inserted into the molecules as indicated in the definitions for each of these groups, being read from left to right. However, in certain cases, one skilled in the art will appreciate
15 that it is possible to prepare compounds of this invention in which these substituents are reversed in orientation relative to the other atoms in the molecule. That is, the substituent to be inserted may be the same as that noted above except that it is inserted into the molecule in the reverse orientation. One skilled in the art will appreciate that these isomeric forms of the compounds of this invention are to be
20 construed as encompassed within the scope of the present invention.

The compounds of the present invention can be used in the form of salts derived from inorganic or organic acids. The salts include, but are not limited to, the following: acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate,
25 cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, palmoate, pectinate, persulfate, 2-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate,
30 thiocyanate, tosylate, mesylate, and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates

like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

5 Examples of acids that may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulfuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, succinic acid and citric acid. Other examples include salts with alkali metals or alkaline earth metals, such as sodium, potassium, calcium or magnesium or
10 with organic bases.

 Also encompassed in the scope of the present invention are pharmaceutically acceptable esters of a carboxylic acid or hydroxyl containing group, including a metabolically labile ester or a prodrug form of a compound of this invention. A metabolically labile ester is one which may produce, for
15 example, an increase in blood levels and prolong the efficacy of the corresponding non-esterified form of the compound. A prodrug form is one which is not in an active form of the molecule as administered but which becomes therapeutically active after some in vivo activity or biotransformation, such as metabolism, for example, enzymatic or hydrolytic cleavage. For a general discussion of prodrugs
20 involving esters see Svensson and Tunek Drug Metabolism Reviews 165 (1988) and Bundgaard Design of Prodrugs, Elsevier (1985). Examples of a masked carboxylate anion include a variety of esters, such as alkyl (for example, methyl, ethyl), cycloalkyl (for example, cyclohexyl), aralkyl (for example, benzyl, p-methoxybenzyl), and alkylcarbonyloxyalkyl (for example, pivaloyloxymethyl).
25 Amines have been masked as arylcarbonyloxymethyl substituted derivatives which are cleaved by esterases in vivo releasing the free drug and formaldehyde (Bundgaard J. Med. Chem. 2503 (1989)). Also, drugs containing an acidic NH group, such as imidazole, imide, indole and the like, have been masked with N-acyloxymethyl groups (Bundgaard Design of Prodrugs, Elsevier (1985)).
30 Hydroxy groups have been masked as esters and ethers. EP 039,051 (Sloan and Little, 4/11/81) discloses Mannich-base hydroxamic acid prodrugs, their preparation and use. Esters of a compound of this invention, may include, for

example, the methyl, ethyl, propyl, and butyl esters, as well as other suitable esters formed between an acidic moiety and a hydroxyl containing moiety.

Metabolically labile esters, may include, for example, methoxymethyl, ethoxymethyl, iso-propoxymethyl, α -methoxyethyl, groups such as α -

5 ((C₁-C₄)alkyloxy)ethyl, for example, methoxyethyl, ethoxyethyl, propoxyethyl, iso-propoxyethyl, etc.; 2-oxo-1,3-dioxolen-4-ylmethyl groups, such as 5-methyl-2-oxo-1,3-dioxolen-4-ylmethyl, etc.; C₁-C₃ alkylthiomethyl groups, for example, methylthiomethyl, ethylthiomethyl, isopropylthiomethyl, etc.; acyloxymethyl groups, for example, pivaloyloxymethyl, α -acetoxymethyl, etc.; ethoxycarbonyl-
10 1-methyl; or α -acyloxy- α -substituted methyl groups, for example α -acetoxylethyl.

Further, the compounds of the invention may exist as crystalline solids which can be crystallized from common solvents such as ethanol, N,N-dimethyl-formamide, water, or the like. Thus, crystalline forms of the compounds of the invention may exist as polymorphs, solvates and/or hydrates of the parent
15 compounds or their pharmaceutically acceptable salts. All of such forms likewise are to be construed as falling within the scope of the invention.

While the compounds of the invention can be administered as the sole active pharmaceutical agent, they can also be used in combination with one or more compounds of the invention or other agents. When administered as a
20 combination, the therapeutic agents can be formulated as separate compositions that are given at the same time or different times, or the therapeutic agents can be given as a single composition.

The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds. Variations and changes which are
25 obvious to one skilled in the art are intended to be within the scope and nature of the invention which are defined in the appended claims.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention
30 to adapt it to various usages and conditions.